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(54) **Title:** NEUROPILIN/VEGF-C/VEGFR-3 MATERIALS AND METHODS

(57) **Abstract:** The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

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NEUROPILIN/VEGF-C/VEGFR-3 MATERIALS AND METHODS

FIELD OF THE INVENTION

The present invention provides materials and methods relating to cellular and molecular biology and medicine, particularly in the areas of vascularization and angiogenesis and the interactions of the vascular system with the nervous system.

BACKGROUND OF THE INVENTION

Interactions of the neuropilin receptor proteins with their ligands in the collapsin/semaphorin family of molecules promotes development of neuronal growth cones and axon guidance, the process which regulates the paths of extending axons during the development of neuronal tissue. Improper retraction of the neural growth cones leads to excess, unwanted innervation of tissue.

Collapsin/semaphorin proteins belong to a family of molecules containing a characteristic semaphorin domain of approximately 500 amino acids in the amino terminus. Over 20 members of the semaphorin family are currently known, both secreted and membrane bound forms, which can be divided into six different subgroups based on primary protein structure. Both secreted and membrane bound semaphorins bind to their receptors as disulfide linked homodimers, and the cytoplasmic tail of membrane bound semaphorins can induce clustering of these ligands in the cell membrane.

Class III semaphorins, secreted proteins which contain the semaphorin domain followed by a C2-type immunoglobulin like domain, have been found to be integrally involved in the repulsion and collapse of neuronal growth cones, a process which prevents improper innervation of dorsal root ganglia, sympathetic neurons, and both cranial and spinal neurons.

Recently, two receptors for the class III semaphorins were identified, neuropilin-1(NRP-1) (Kolodkin et al, Cell. 90:753-762. 1997 and He et al, Cell. 90:739-51. 1997) and neuropilin-2 (NRP-2) (Chen et al, Neuron, 19:547. 1997). Neuropilin-1, a type-I membrane protein originally isolated from the Xenopus

nervous system, was identified by semaphorin III receptor expression cloning, as a high affinity receptor for Sema III and other semaphorin family members. Further analysis by PCR using sequences homologous to neuropilin-1 identified a related receptor, neuropilin-2, which shows approximately 44% homology to NRP-1 throughout the entire protein length.

The extracellular portion of both NRP-1 and NRP-2 shows an interesting mix of cell binding domains, possessing five distinct protein domains designated a1/a2, b1/b2, and c. The a1/a2 (CUB) domains resemble protein sequences found in complement components C1r and Cs while the b1/b2 domains are similar to domains found in coagulation factors V and VIII. The central portion of the c domain, similar to the meprin/A5/mu-phosphotase (MAM) homology domain, is important for neuropilin dimerization. The intracellular region of neuropilins contains a transmembrane domain and a short, highly conserved cytoplasmic tail of ~43 amino acids that possesses no known catalytic activity to date. Both the a1/a2 and b1/b2 domains are necessary to facilitate semaphorin binding to neuropilins.

Since the short cytoplasmic tail of neuropilins does not possess signaling capabilities, neuropilins probably couple with other receptors to transmit intracellular signals as a result of semaphorin binding. Investigation of this scenario concluded that neuropilins interact with another family of semaphorin receptors, the plexins, which possess a cytoplasmic tail containing a sex-plexin domain capable of undergoing phosphorylation and initiating downstream signaling cascades (Tamagnone et al Trends in Cell Biol, 10:377-83. 2000). Plexins were originally isolated as orphan receptors for membrane bound semaphorins, and plexins alone are incapable of binding secreted semaphorins such as those in the class III subfamily. A great deal of evidence now demonstrates that class III semaphorin binding is mediated through a receptor complex which includes homo- or heterodimeric neuropilins and a plexin molecule needed to transduce intracellular signals. Interactions of plexins with neuropilins confers specificity of semaphorin binding and can also increase the binding affinity of these ligands. Signaling of semaphorins through their receptors is reviewed in Fujisawa et al, (Current Opinion in Neurobiology, 8:587. 1998) and Tamagnone et al, (Trends in Cell Biol, 10:377. 2000).

Neuropilin-1 (Tagaki et al., Neuron 7:295-307. 1991; Fujisawa et al., Cell Tissue Res. 290:465-70. 1997), a 140 kD protein whose gene is localized to

chromosome 10p12 (Rossingnol et al., Genomics 57:459-60. 1999), is expressed in a wide variety of tissues during development, including nervous tissue, capillaries and vessels of the cardiovascular system, and skeletal tissue, and persists in many adult tissues, most notably the placenta and heart. In addition to binding Sema3A, NRP-1 also binds several other semaphorin family members including Sema3B, Sema3C (SemaE), and Sema3F (SemaIV) (with low affinity) (He et al., Cell 90:739-51. 1997; Kolodkin et al.,Cell 90:753-62. 1997). Mice homozygous mutant at the NRP-1 locus demonstrate defects not only in axonal guidance but also show altered vascularization in the brain and defects in the formation of large vessels of the heart (Kawasaki et al, Development 126:4895. 1990). Interestingly, NRP-1 overexpression in embryos leads to excess capillary and vessel formation and hemorrhaging, implicating a role for NRP-1 in vascular development (Kitsukawa et al, Development, 121:4309. 1995).

Recent evidence shows that neuropilin-1 can act as a receptor for an isoform of vascular endothelial growth factor (VEGF/VEGF-A) (Soker et al, Cell 92:735. 1998), which is a key mediator of vasculogenesis and angiogenesis in embryonic development (reviewed in Robinson et al, J. Cell Science. 114:853-65) and also plays a significant role in tumor angiogenesis. Binding of VEGF to receptor tyrosine kinases (RTK) VEGFR-1 and VEGFR-2 facilitates vascular development. Both the non-heparin dependent $VEGF_{121}$ isoform and the heparin-binding $VEGF_{165}$ bind VEGFR-2 with the same affinity in vitro, but do not elicit equivalent biochemical responses, indicating that additional factors mediate VEGFR-2 activation (Whitaker et al, J Bio Chem. 276:25520-31. 2001). Analysis of the binding of several splice variants of VEGF reveal that NRP-1 does not bind the $VEGF_{121}$ isoform but selectively binds the $VEGF_{165}$ variant in a heparin- dependent manner within the b domain of NRP-1 (Giger et al, Neuron 21:1079-92. 1998). NRP-1 demonstrates a binding affinity for the $VEGF_{165}$ isoform comparable to that of it's Sema3A ligand. This differential affinity of NRP-1 for $VEGF_{165}$ may explain the signaling capabilities of this splice variant over the non-heparin binding $VEGF_{121}$ and may indicate that neuropilin-1 interacts with VEGFR-2 as a co-receptor in VEGF binding (Whitaker et al., 2001), similar to its role in plexin/semaphorin complexes. $VEGF_{165}$ binds NRP-1 through VEGF exon 7, which confers heparin binding affinity to this molecule, and is lacking in the $VEGF_{121}$ isoform. NRP-1 also binds other VEGF family members,

VEGF-B and placenta growth factor (PlGF-2) (Migdal et al, J. Biol.Chem. 273:22272-78. 1998; Makinen et al, J. Biol. Chem. 274: 21217-222. 1999).

Neuropilin-2 (Chen et al, Neuron 19:547-59. 1997), a 120 kD protein whose gene is localized to chromosome 2q34 (Rossingnol et al., Genomics 57:459-60. 1999), exhibits similar tissue distribution in the developing embryo as neuropilin-1, but does not appear to be expressed in endothelial cells of capillaries (Chen et al, Neuron 19:547-59. 1997). NRP-2 is also a semaphorin receptor, binding Sema3F with high affinity, Sema3C with affinity comparable to Sema3C/NRP-1 binding, NRP-2 also appears to interact with very low affinity to Sema3A (Kolodkin et al.,Cell 90:753-62. 1997). NRP-2 deficient mice survive embryogenesis with no apparent vascular defects, but exhibit defects in the Sema3F-dependent formation of sympathetic and hippocampal neurons and defects in axonal projections in the peripheral and central nervous systems, implicating NRP-2 in axonal guidance (Chen et al, Neuron 25:43-56. 2000; Giger et al, Neuron 25:29-41. 2000) and suggesting distinct roles for NRP-1 and NRP-2 in development. NRP-2 expression has also been noted in sites that innervate smooth muscle cells such as mesentery, muscular, and submucosal plexuses (Cohen et al, Biochem Biophy Res Comm. 284:395-403. 2001).

Experimental evidence establishes that, similar to NRP-1, neuropilin-2 preferentially binds $VEGF_{165}$, and shows additional binding to the $VEGF_{145}$ isoform, another heparin-binding splice variant of VEGF (Gluzman-Poltorak et al, J. Biol Chem. 275:18040-45. 2000). Neuropilin-2 interaction with the $VEGF_{145}$ splice variant, which lacks exon 7, is mediated through $VEGF_{145}$ exon 6 which , like exon 7, is capable of mediating heparin binding activity. $VEGF_{145}$ cannot bind NRP-1, which further supports the theory of differential functions for neuropilin-1 and neuropilin-2 in vascular development. $VEGF_{145}$ was originally isolated from carcinomas of the female reproductive tract (Pavelock et al, Endocrinology. 142: 613-22. 2001) where neuropilin-2 expression shows differential regulation in response to hormonal changes as compared to NRP-1 and VEGFR-2. The co-expression of both neuropilins, VEGFs, and VEGFRs in a particular cell type may be indicative of a potential receptor/ligand complex formation and needs to be investigated in greater detail.

VEGF/VEGFR interactions play an intergral role in embryonic vasculogenesis and angiogenesis, as well as a role in adult tissue neovascularization during wound healing, remodeling of the female reproductive system, and tumor

growth. Elucidating additional factors involved in the regulation of neovascularization and angiogenesis, as well as their roles in such processes, would aid in the development of therapies directed toward prevention of vascularization of solid tumors and induction of tumor regression, and induction of vascularization to promote faster, more efficient wound healing after injury, surgery, or tissue transplantation, or to treat ischemia by inducing angiogenesis and arteriogenesis of vessels that nourish the ischemic tissue. In fact, modulation of angiogenic processes may be instrumental in treatment or cure of many of the most significant diseases that plague humans in the developed world, such as cerebral infarction/bleeding, acute myocardial infarction and ischemia, and cancers. Modulation of neuronal growth also is instrumental in treatment of numerous congenital, degenerative, and trauma-related neurological conditions. The newfound interaction between neuropilins and VEGF provided one target for intervention at a molecular level for both neuronal and vascular diseases and conditions. However, the ability to develop targeted therapies is complicated by the existence of multiple binding partners for neuropilins. There exists a need to delineate molecules that bind neuropilins in order to permit identification of modulation of neuropilin activities and to optimize the specificity of such molecules to optimize therapies in areas of unwanted angiogenesis, as in cancers or solid tumor growth, and potentiate pro–angiogenic properties to promote and speed needed blood vessel growth, as in wound healing; and optimize therapies directed to neuronal growth and organization.

SUMMARY OF THE INVENTION

The present invention addresses one or more needs in the art relating to modulation of angiogenic and nervous system growth and function, by identifying novel molecular interactions between neuropilins and VEGF-C molecules, and between neuropilins and VEGFR-3 molecules. These newly delineated interactions facilitate identification of novel materials and methods for modulating both angiogenic processes (including lymphangiogenic processes) and processes involved in neural cell regeneration. The newly delineated interactions also facilitate better therapeutic targeting by permitting design of molecules that modulate single receptor-ligand interactions highly selectively, or molecules that modulate multiple interactions.

For example, the discovery of VEGF-C-neuropilin interactions provides novel screening assays to identify new therapeutic molecules to modulate (up-regulate/activate/stimulate or downregulate/inhibit) VEGF-C-neuropilin interactions. Such molecules are useful as therapeutics (and/or as lead compounds) for diseases and conditions in which VEGF-C/neuropilin interactions have an influence, including those in which lymphatic or blood vessel growth play a role.

In one embodiment, the invention provides a method for identifying a modulator of binding between a neuropilin receptor and VEGF-C polypeptide comprising steps of:

a) contacting a neuropilin composition that comprises a neuropilin polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;

b) detecting binding between neuropilin polypeptide and VEGF-C polypeptide in the presence and absence of the putative modulator; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

In one variation, the method further includes a step (d) of making a modulator composition by formulating a modulator identified according to step (c) in a carrier, preferably a pharmaceutically acceptable carrier. A modulator so formulated is useful in animal studies and also as a therapeutic for administration to image tissues or treat diseases associated with neuropilin- VEGF-C interactions, wherein the administration of a compound could interfere with detrimental activity of these molecules, or promote beneficial activity. Thus, in still another variation, the method further includes a step (e) of administering the modulator composition to an animal that comprises cells that express the neuropilin receptor, and determining physiological effects of the modulator composition in the animal. The animal may be human, or any animal model for human medical research, or an animal of importance as livestock or pets. In a preferred variation, the animal (including humans) has a disease or condition characterized by aberrant neuropilin-2/VEGF-C biology, and the

modulator improves the animal's state (e.g., by reducing disease symptoms, slowing disease progression, curing the disease, or otherwise improving clinical outcome).

Step (a) of the foregoing methods involves contacting a neuropilin composition with a VEGF-C composition in the presence and absence of a compound. By "neuropilin composition" is meant any composition that includes a whole neuropilin receptor polypeptide, or includes at least the portion of the neuropilin polypeptide needed for the particular assay - in this case the portion of the neuropilin polypeptide involved in VEGF-C binding. Exemplary neuropilin compositions include: (i) a composition comprising a purified polypeptide that comprises an entire neuropilin protein or that comprises a neuropilin receptor extracellular domain fragment that binds VEGF-C polypeptides; (ii) a composition containing phospholipid membranes that contain neuropilin receptor polypeptides on their surface; (iii) a living cell recombinantly modified to express increased amounts of a neuropilin receptor polypeptide on its surface (e.g., by inserting a neuropilin gene, preferably with an attached promoter, into a cell; or by amplifying an endogenous neuropilin gene; or by inserting an exogenous promoter or other regulatory sequence to up-regulate an endogenous neuropilin gene); and (iv) any isolated cell or tissue that naturally expresses the neuropilin receptor polypeptide on its surface. For certain assay formats, it may be desirable to bind the neuropilin molecule of interest (e.g., a composition comprising a polypeptide comprising a neuropilin receptor extracellular domain fragment) to a solid support such as a bead or assay plate well. "Neuropilin composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated wherein the neuropilin polypeptide is fused to another protein (such as an antibody Fc fragment) to improve solubility, or to provide a marker epitope, or serve any other purpose. For other assay formats, soluble neuropilin peptides may be preferred. In one preferred variation, the neuropilin composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment fused to an immunoglobulin Fc fragment. Although two family members are currently known, neuropilin-1 and neuropilin-2, practice of the invention with other neuropilin receptor family members that are subsequently discovered is contemplated. The neuropilin receptor chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the

chosen neuropilin receptor is identical in amino acid sequence to the native receptor, it will be apparent that the invention can still be practiced if variations have been introduced in the neuropilin sequence that do not eliminate its VEGF-C binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated.

VEGF-C molecules occur naturally as secreted factors that undergo several enzymatic cleavage reactions before release into te surrounding milieu. Thus, "VEGF-C composition" means any composition that includes a prepro-VEGF-C polypeptide, the intermediate and final cleavage products of prepro-VEGF-C, ΔNΔCVEGF-C, or includes at least the portion of the VEGF-C needed for the particular assay - in this case the portion involved in binding to a neuropilin receptor. Exemplary VEGF-C compositions include: (i) a composition comprising purified complete prepro-VEGF-C polypeptide or comprising a prepro-VEGF-C polypeptide fragment that binds the neuropilin receptor chosen for the assay; and (ii) conditioned media from a cell that secretes the VEGF-C protein. For certain assay formats, it may be desirable to bind the VEGF-C molecule of interest (e.g., a polypeptide comprising VEGF-C fragment) to a solid support such as a bead or assay plate well. "VEGF-C composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated. The data provided herein establishes that isoforms of VEGF-C bind both neuropilin-1 and neuropilin-2. The VEGF-C polypeptide chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. In one embodiment the VEGF-C sompositons comprises a fragment of human prepro-VEGF-C that contains amino acids 103-227 of SEQ. ID NO.: 24. In another embodiment, the VEGF-C composition comprises amino acids 32-227 of the human prepro-VEGF-C sequence of SEQ. ID NO.: 24. While it will be apparent that the assay will likely give its best results if the functional portion of the chosen VEGF-C is identical in amino acid sequence to the corresponding portion of the native VEGF-C, it will be apparent that the invention can still be practiced if variations have been introduced in the VEGF-C sequence that do not eliminate its neuropilin receptor binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated.

The putative modulator compound that is employed in step (a) can be any organic or inorganic chemical or biological molecule or composition of matter that one would want to test for ability to modulate neuropilin-VEGF-C interactions. Since the most preferred modulators will be those that can be administered as therapeutics, it will be apparent that molecules with limited toxicity are preferred. However, toxicity can be screened in subsequent assays, and can be "designed out" of compounds by pharmaceutical chemists. Screening of chemical libraries such as those customarily kept by pharmaceutical companies, or combinatorial libraries, peptide libraries, and the like is specifically contemplated.

Step (b) of the above-described method includes detecting binding between neuropilin and VEGF-C in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. Techniques that provide quantitative measurements of binding are preferred. For example, one or both of neuropilin/VEGF-C may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate quantitative detection with standard laboratory machinery and techniques. Immunoassays represent a common and highly effective body of techniques for detecting binding between two molecules.

When the neuropilin composition comprises a cell that expresses neuropilin naturally or recombinantly on its surface, it will often be possible to detect VEGF-C binding indirectly, e.g., by detecting or measuring a VEGF-C binding-induced physiological change in the cell. Such possible changes include phosphorylation of the neuropilin associated VEGF-receptor; cell chemotaxis; cell growth; DNA synthesis; changes in cellular morphology; ionic fluxes; or the like.

Step (c) of the outlined method involves identifying a modulator compound on the basis of increased or decreased binding between the neuropilin receptor polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound as compared to such binding in the absence of the putative modulator compound. Generally, more attractive modulators are those that will activate or inhibit neuropilin-VEGF-C binding at low concentrations, thereby permitting use of the modulators in a pharmaceutical composition at lower effective doses.

As described below in greater detail, the growth factor VEGF-D shares amino acid sequence similarity to VEGF-C, and is known to undergo similar proteolytic processing from a prepro-VEGF-D form into smaller, secreted growth factor forms, and is known to share two VEGFR receptors with VEGF-C, namely, VEGFR-3 and VEGFR-2. Due to these and other similarities, it is expected that VEGF-D binds neuropilins in a manner analogous to what has been shown with VEGF-C, and such binding may be confirmed with assays described in the examples (by substituting VEGF-D). Accordingly, as another aspect of the invention, practice of the above-described screening method (and other methods described in the ensuing paragraphs) is contemplated wherein VEGF-D polypeptides are employed in lieu of VEGF-C polypeptides. A detailed description of the human VEGF-D gene and protein are provided in Achen, et al., Proc. Nat'l Acad. Sci. U.S.A., 95(2): 548-553 (1998); International Patent Publication No. WO 98/07832, published 26 February 1998; and in Genbank Accession No. AJ000185, all incorporated herein by reference.

In another embodiment, the invention provides a method for screening for selectivity of a modulator of VEGF-C biological activity. The term "selectivity" - when used herein to describe modulators - refers to the ability of a modulator to modulate one protein-protein interaction (e.g., VEGF-C binding with neuropilin-2) with minimal effects on the interaction of another protein-protein interaction of one or more of the binding pairs (e.g., VEGF-C binding with VEGFR-2, or VEGFR-3, or neuropilin-1). More selective modulators significantly alter the first protein-protein interaction with minimal effects on the other protein-protein interaction, whereas non-selective modulators will alter two or more protein-protein interactions. It will be appreciated that selectivity is of immense interest to the design of effective pharmaceuticals. For example, in some circumstances, it may be desirable to identify modulators that alter VEGF-C/neuropilin interactions but not semaphorin/neuropilin interactions, because one wishes to modulate vessel growth but not neurological growth. It may be desirable in some circumstances to non-selectively inhibit all VEGF-C related activities, e.g., in anti-tumor therapy. The molecular interactions identified herein permit novel screening assays to help identify the selectivity of modulators.

For example, VEGF-C molecules are also known ligands for the VEGFR-2 and VEGFR-3 tyrosine kinase receptors. VEGF-C/VEGFR-3 interactions

appear to be integrally involved in the development and maintenance of lymphatic vasculature and may also be involved in cancer metastasis through the lymphatic system. In one instance it may be beneficial to modulate VEGF-C/neuropilin interactions specifically while in another instance it may be useful to selectively modulate the VEGF-C/VEGFR interactions. The present invention provides counterscreen assays that identify the selectivity of a modulator for neuropilin-VEGF-C binding or VEGF-C-VEGFR binding.

Thus, in one variation, the invention provides a method, comprising steps of:

a) contacting a VEGF-C composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin (in the compositions) in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the neuropilin;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGFR-3 extracellular domain; and

(ii) a polypeptide comprising a VEGFR-2 extracellular domain; and

(c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

Step (a) of the above embodiment involves contacting a neuropilin composition with a VEGF-C compostion as described previosuly. Step (b) of the outlined method involves contacting a VEGF-C composition as described in step (a) with a composition comprising a VEGF-C binding partner in the presence and in the

absence of the same compound. The VEGF-C binding partner is selected from the group consisting of: (i) a polypeptide comprising a VEGFR-3 extracellular domain; and (ii) a polypeptide comprising a VEGFR-2 extracellular domain. Thus, the above-described embodiment involves measuring selectivity of a modulator of VEGF-C/neuropilin binding in relation to VEGF-C binding to its receptors, VEGFR-2 and VEGFR-3. The VEGF-C binding partner chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the chosen VEGF-C binding partner is identical in amino acid sequence to the native VEGF-C binding partner, it will be apparent that the invention can still be practiced if variations have been introduced in the VEGF-C binding partner sequence that do not eliminate its VEGF-C binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated. Any technique for detecting intermolecular binding may be employed. For example, one or both of the binding partner or the VEGF-C may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a die, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

In one variation, the binding partner composition comprises a cell that expresses the binding partner naturally or recombinantly on its surface. In this situation, it will often be possible to detect VEGF-C binding indirectly, e.g., by detecting or measuring a VEGF-C binding-induced physiological change in the cell. Such possible changes include phosphorylation of the associated VEGFR; cell chemotaxis; cell growth, changes in cellular morphology; ionic fluxes, or the like.

Step (c) of the outlined method involves identifying the selectivity of the modulator compound on the basis of increased or decreased binding in steps (a) and (b). A compound that is a selective modulator causes significant differential binding in either step (a) or step (b), but does not cause significant differential binding in both steps (a) and (b). A non-specific modulator causes significant differential binding in both steps (a) and (b).

In still another embodiment, the invention provides a method for screening for selectivity of a modulator of neuropilin biological activity, comprising steps of:

a) contacting a neuropilin composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the VEGF-C;

b) contacting a neuropilin composition with a composition comprising a neuropilin binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising an amino acid sequence of a semaphorin 3 polypeptide,

(ii) a polypeptide comprising a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and

(iii) a polypeptide comprising an amino acid sequence of a plexin polypeptide

d) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

Step (a) of the above embodiment involves contacting a neuropilin composition with a VEGF-C compostion as described previously. Step (b) of the outlined method involves contacting a neuropilin composition as described in step (a) with a composition comprising a neuropilin binding partner in the presence and in the absence of a compound. The neuropilin binding partner comprises any protein other than VEGF-C that the neuropilin binds. Exemplary binding partners include the following polypeptides: a polypeptide comprising the amino acid sequence of a

semaphorin 3family member polypeptide; a polypeptide comprising a VEGF-A amino acid sequence, a polypeptide comprising a VEGF-B amino acid sequence, a polypeptide comprising a VEGF-D amino acid sequence, a polypeptide comprising a PlGF-2 amino acid sequence, a polypeptide comprising a VEGFR-1 amino acid sequence, a polypeptide comprising a VEGFR-2 amino acid sequence, a polypeptide comprising a VEGFR-3 amino acid sequence; and a polypeptide comprising the amino acid sequence of a plexin family member. The binding partners chosen are preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the chosen neuropilin binding partner is identical in amino acid sequence to the native sequence, it will be apparent that the invention can still be practiced if variations have been introduced in the native sequence that do not eliminate its neuropilin binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated.

The above-described method includes detecting binding between the neuropilin composition and the binding partner in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. For example, one or both of the binding partner or the neuropilin may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

Step (c) of the outlined method involves identifying the selectivity of the modulator compound on the basis of increased or decreased binding in steps (a) and (b), and having the characteristics of a selective modulator compound as described previously.

In an additional embodiment, the invention provides a method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

Step (a) of the aforementioned method involves contacting a neuropilin composition as described with a VEGFR-3 composition in the presence and absence of a putative modulator compound. The neuropilin composition contemplated is described previously. A VEGFR-3 composition comprises a member selected from the group consisting of (i) a composition comprising a purified polypeptide that comprises an entire VEGFR-3 protein or that comprises a VEGFR-3 fragment that binds the neuropilin; (ii) a composition containing phospholipid membranes that contain VEGFR-3 polypeptides on their surface; (iii) a living cell recombinantly modified to express increased amounts of a VEGFR-3 on its surface; and (iv) any isolated cell or tissue that naturally expresses the VEGFR-3 on its surface. For certain assay formats, it may be desirable to bind the VEGFR-3 molecule of interest (e.g., a polypeptide comprising a VEGFR-3 extracellular domain fragment) to a solid support such as a bead or assay plate well. "VEGFR-3 composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated. For other assay formats, soluble VEGFR-3 peptides may be preferred. In one preferred variation, the VEGFR-3 receptor composition comprises a VEGFR-3 receptor fragment fused to an immunoglobulin Fc fragment.

Step (b) of the above method involves detecting binding between the neuropilin composition and the VEGFR-3 composition in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. For example, one or both of neuropilin/VEGFR-3 may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

Generally, more attractive modulators are those that will activate or inhibit neuropilin-VEGFR-3 binding at lower concentrations, thereby permitting use of the modulators in a pharmaceutical composition at lower effective doses.

In another embodiment, the invention provides for a method for screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and

(ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

A selective modulator causes significant differential binding in either step (a) or step (b), but does not cause significant differential binding in both steps (a) and (b).

It will be apparent that the foregoing selectivity screens represent only a portion of the specific selectivity screens of the present invention, because the neuropilins, VEGF-C, VEGF-D, and VEGFR-3 all have multiple binding partners, creating a number of permutations for selectivity screens. Any selectivity screen that involves looking at one of the following interactions: (i) neuropilin-1/VEGF-C; (ii) neuropilin-1/VEGF-D; (iii) neuropilin-2/VEGF-C; (iv) neuropilin-2/VEGF-D; (v)

neuropilin-1/VEGFR-3; and (vi) neuropilin-2/VEGFR3; together with at least one other interaction (e.g., a known interaction of one of these molecules, or a second interaction from the foregoing list) is specifically contemplated as part of the present invention.

Likewise, all of the screens for modulators and the selectivity screens optionally comprising one or both of the following steps: (1) making a modulator composition by formulating a chosen modulator in a pharmaceutically acceptable carrier; and (2) administering the modulator so formulated to an animal or human and determining the effect of the modulator. Preferably, the animal or human has a disease or condition involving one of the foregoing molecular interactions, and the animal or human is monitored to determine the effect of the modulator on the disease or condition, which, hopefully, is ameliorated or cured.

The discovery of neuropilin-2 and neuropilin-1 binding to VEGF-C molecules provides new and useful materials and methods for investigating biological processes involved in many currently known disease states. For example, the invention provides for a method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a neuropilin polypeptide or fragment thereof that binds to a VEGF-C polypeptide;

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin in the mammalian organism. Administration of soluble forms of the neuropilin is preferred.

Preferably, the mammalian organism is human. Also, the cells preferably comprise vascular endothelial cells, especially cells of lymphatic origin, such as human microvascular endothelial cells (HMVEC) and human cutaneous fat pad microvascular cells (HUCEC). In a highly preferred embodiment, the organism has a disease characterized by aberrant growth, migration, or proliferation of endothelial cells. The administration of the agent beneficially alters the aberrant

growth, migration, or proliferation, e.g., by correcting it, or reducing its severity, or reducing its deleterious symptoms or effects.

For example, in one variation, the animal has a cancer, especially a cancerous tumor characterized by vasculature containing neuropilin-expressing endothelial cells. A composition is selected that will decrease growth, migration, or proliferation of the cells, and thereby retard the growth of the tumor by preventing growth of new vasculature. In such circumstances, one may wish to administer agents that inhibit other endothelial growth factor/receptor interactions, such as inhibitors of the VEGF-family of ligands; endostatins; inhibitory angiopoietins, or the like. Exemplary inhibitors include antibody substances specific for the growth factors or their ligands. The invention further contemplates treating lymphangioamas, lymphangiosarcomas, and metastatic tumors, which exhibit VEGFR-3 expressing vascular endothlial cells or VEGFR-3 expressing lymphatic endothelial cells. In one embodiment, administration of a composition that inhibits the interaction of VEGFR-3 with its ligand diminishes or abolishes lymphangiogenesis and retards the spread of cancerous cells. In an additional embodiment, administration of a composition that stimulates the interaction of VEGFR-3 with its ligand enhances lymphangiogenesis and speeds wound healing.

Further contemplated is a method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide, wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor in the mammalian organism. In an alternative embodiment, the bispecific antibody is specific for the neuropilin receptorand for aVEGFR-3 polypeptide.

In one embodiment ,the invention provides a bispecific antibody which specifically binds a neuropilin receptor and a VEGF-C polypeptide. Alternatively, the

invention provides a bispecific antibody which specifically binds to the neuropilin receptor and a VEGFR-3 polypeptide.

In another embodiment, the invention can also be used to inhibit neural degeneration in the central nervous system. Development of scars surrounding neuronal injury in either the peripheral and more specifically the central nervous system has been associated with constitutive expression of the semaphorin ligands. Also, upregulation of Sema3F, a primary ligand for the neuropilin-2 receptor, has been detected in the brains of Alzheimer's patients. The present invention provides for a means to alter the semaphorin-neuropilin interactions using VEGF-C compositions that specifically interfere with semaphorin activity in the nervous system.

For example, the invention provides for a method of modulating aberrant growth, or neuronal scarring in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having neuronal cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin receptor;

wherein the composition is administered in an amount effective to reduce neuronal scarring in cells that express neuropilin in the mammalian organism.

Other conditions to treat include inflammatory diseases (e.g., Rheumatoid arthritis, chronic wounds and atherosclerosis).

Similarly, the invention provides a polypeptide comprising a fragment of VEGF-C that binds to a neuropilin receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor.

Likewise, the invention provides a polypeptide comprising a fragment of a neuropilin that binds to a VEGF-C, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor. Soluble forms of the neuropilin, lacking the transmembrane domain, are preferred. The invention also

provides for a polypeptide comprising a fragment of a neuropilin receptor that binds to a VEGFR-3 polypeptide, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a VEGFR-3 polypeptide.

With respect to aspects of the invention that involve administration of protein agents to mammals, a related aspect of the invention comprises gene therapy whereby a gene encoding the protein of interest is administered in a manner to effect expression of the protein of interest in the animal. For example, the gene of interest is attached to a suitable promoter to promote expression of the protein in the target cell of interest, and is delivered in any gene therapy vector capable of delivering the gene to the cell, including adenovirus vectors, adeno-associated virus vectors, liposomes, naked DNA transfer, and others.

Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, and all such features are intended as aspects of the invention.

Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

In addition to the foregoing, the invention includes, as an additional aspect, all embodiments of the invention narrower in scope in any way than the variations specifically mentioned above. Although the applicant(s) invented the full scope of the claims appended hereto, the claims appended hereto are not intended to encompass within their scope the prior art work of others. Therefore, in the event that statutory prior art within the scope of a claim is brought to the attention of the applicants by a Patent Office or other entity or individual, the applicant(s) reserve the right to exercise amendment rights under applicable patent laws to redefine the subject matter of such a claim to specifically exclude such statutory prior art or obvious variations of statutory prior art from the scope of such a claim. Variations of

the invention defined by such amended claims also are intended as aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the construction of the neuropilin-2 IgG fusion protein a17 and a22 expression vectors.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based, in part, on the discovery of novel interaction between proteins that have previously been characterized in the literature, but whose interactions were not previously appreciated. A number of the molecules are explicitly set forth with annotations to the Genbank database or to a Sequence Listing appended hereto, but it will be appreciated that sequences for species homologous ("orthologs") are also easily retrieved from databases and/or isolated from natural sources. Thus, the following table and description should be considered exemplary and not limiting.

A. Molecules of interest to the present invention.*

Molecule	Genbank Accession #	SEQ ID NO.
Neuropilin-1	NM003873	1 and 2
Soluble Neuropilin-1, s11	AF280547	
Neuropilin-2 [a(17)]	NM003872	3 and 4
a(0)	AF022859	
a(17)	AF022860	
b(0)	AF280544	
b(5)	AF280545	
Soluble Neuropilin-2, s9	AF280546	
Murine neuropilin-1	D50086	5 and 6

Molecule	Genbank Accession #	SEQ ID NO.
Murine neuropilin-2		
a(0)	AF022854	
a(5)	AF022861	
a(17)	AF022855	7 and 8
a(22)	AF022856	
b(0)	AF022857	
b(5)	AF022858	
Semaphorin 3A	NM006080	9 and 10
Semaphorin 3B	NM004636	11 and 12
Semaphorin 3C	NM006379	13 and 14
Semaphorin 3E	NM012431	15 and 16
Semaphorin 3F	NM004186	17 and 18
VEGF-A	Q16889	19 and 20
VEGF165	M32977	
VEGF-B	U48801	21 and 22
VEGF-C	X94216	23 and 24
VEGF-D	AJ000185	25 and 26
VEGF-E	S67522	
PlGF	NM002632	27 and 28
VEGFR-1	X51602	
VEGFR-2	L04947	29 and 30
VEGFR-3	X68203	31 and 32
Plexin-A1	X87832	
Plexin-A2	NM025179	

Molecule	Genbank Accession #	SEQ ID NO.
PDGF-A,-B,-C	NM002607; NM002608; NM016205	
PDGFR-A,-B	NM006206; NM002609	

* All Sequences of Human origin unless otherwise noted.

The Neuropilin Family

The neuropilin-1 and neuropilin-2 genes span over 120 and 112 kb, respectively, and are comprised of 17 exons, five of which are identical in size in both genes, suggesting genetic duplication of these genes (Rossignol et al, Genomics 70:211-22. 2000). Several splice variants of the neuropilins have been isolated to date, the functional significance of which is currently under investigation.

Isoforms of NRP-2, designated NRP2a and NRP2b, were first isolated from the mouse genome (Chen et al, Neuron 19:547-59. 1997). In mouse, NRP2a isoforms contain insertions of 0, 5, 17, or 22 (5 + 17) amino acids after amino acid 809 of NRP-2 and are named NRP2a(0) (Genbank Accession No. AF022854)(SEQ ID NO. 7 and 8), NRP2a(5) (Genbank Accession No. AF022861), NRP2a(17) (Genbank Accession No. AF022855), and NRP2a(22)(Genbank Accession No. AF022856), respectively. Only two human NRP2a isoforms homologous to the mouse variants NRP2a(17) (Genbank Accession No. AF022860) (SEQ ID NO. 3 and 4) and NRP2a(22), have been elucidated. The human a(22) isoform contains a five amino acid insertion, sequence GENFK, after amino acid 808 in NRP2a(17). Tissue analysis of brain, heart, lung, kidney liver and placenta shows that the a(17) isoform is more abundant in all of these sites.

The human NRP2b isoforms appear to express an additional exon, designated exon 16b, not present in either NRP2a or NRP-1. Two human NRP2b isoforms homologous to mouse NRP2b(0) (Genbank Accession No. AF022857) and NRP2b(5) (Genbank Accession No. AF022858) have been identified which contain either a 0 or 5 amino acid insert (GENFK) after amino acid 808 in NRP2b(0) (Rossignol et al., Genomics 70:211-22. 2000). Tissue distribution analysis demonstrates a higher expression of human NRP2b(0) (Genbank Accession No. AF280544) over NRP2b(5) (Genbank Accession No. AF280545) in adult brain, heart,

lung, kidney, liver, and placenta. The NRP2a and NRP2b isoforms demonstrate divergence in their C terminal end, after amino acid 808 of NRP2 which is in the linker region between the c domain and the transmembrane domain. This differential splicing may lead to the difference seen in tissue expression of the two isoforms, where NRP2a is expressed more abundantly in the placenta, liver, and lung with only detectable levels of NRP2b, while NRP2b is found in skeletal muscle where NRP2a expression is low. Both isoforms are expressed in heart and small intestine.

In addition to genetic isoforms of the neuropilins, truncated soluble forms of the proteins have also been cloned (Gagnon et al, Proc. Natl. Acad. Sci USA 97:2573-78 2000; Rossignol et al, Genomics 70:211-22. 2000). Naturally occurring truncated forms of the NRP-1 protein, s11NRP1 (Genbank Accession No. AF280547) and s12NRP1, have been cloned, that encode 704 and 644 amino acid neuropilin-1, respectively, and contain the a and b domains but not the c domain. The s12NRP1 variant is generated by pre-mRNA processing in intron 12. The s11NRP1 truncation occurs after amino acid 621 and lacks the 20 amino acids encoded by exon 12, but contains coding sequence found within intron 11 that gives it 83 novel amino acids at the C-terminus. This intron derived sequence does not contain any homology to known proteins.

A natural, soluble form of NRP-2 has also been identified which encodes a 555 amino acid protein containing the a domains, b1 domain, and part of the b2 domain, lacking the last 48 amino acids of this region. The truncation occurs after amino acid 547 within intron 9, thus the protein has been named s9NRP2 (Genbank Accession No. AF2805446), and adds 8 novel amino acids derived from the intron cleavage (VGCSVWRPL) at the C-terminus. Gagnon et al (Proc. Natl. Acad. Sci USA 97:2573-78. 2000) report that soluble neuropilin-1 isoform s12NRP1 is capable of binding VEGF165 equivalent to the full length protein, but acts as an antagonist of VEGF165 binding, inhibiting VEGF165 activity and showing anti-tumor properties in a rat prostate carcinoma model.

The PDGF/VEGF Family

The PDGF/VEGF family of growth factors includes at least the following members: PDGF-A (see e.g., GenBank Acc. No. X06374), PDGF-B (see e.g., GenBank Acc. No. M12783), VEGF (see e.g., GenBank Acc. No. Q16889 referred to herein for clarity as VEGF-A or by particular isoform), PlGF (see e.g.,

GenBank Acc. No. X54936 placental growth factor), VEGF-B (see e.g., GenBank Acc. No. U48801; also known as VEGF-related factor (VRF)), VEGF-C (see e.g., GenBank Acc. No. X94216; also known as VEGF related protein (VRP or VEGF-2)), VEGF-D (also known as c-fos-induced growth factor (FIGF); see e.g., Genbank Acc. No. AJ000185), VEGF-E (also known as NZ7 VEGF or OV NZ7; see e.g., GenBank Acc. No. S67522), NZ2 VEGF (also known as OV NZ2; see e.g., GenBank Acc. No. S67520), D1701 VEGF-like protein (see e.g., GenBank Acc. No. AF106020; Meyer et al., EMBO J 18:363-374), and NZ10 VEGF-like protein (described in International Patent Application PCT/US99/25869) [Stacker and Achen, Growth Factors 17:1-11 (1999); Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)]. The PDGF/VEGF family proteins are predominantly secreted glycoproteins that form either disulfide-linked or non-covalently bound homo- or heterodimers whose subunits are arranged in an anti-parallel manner [Stacker and Achen, Growth Factors 17:1-11 (1999); Muller et al., Structure 5:1325-1338 (1997)].

The VEGF subfamily is composed of PDGF/VEGF members which share a VEGF homology domain (VHD) characterized by the sequence: C-X(22-24)-P-[PSR]-C-V-X(3)-R-C-[GSTA]-G-C-C-X(6)-C-X(32-41)-C.

VEGF-A was originally purified from several sources on the basis of its mitogenic activity toward endothelial cells, and also by its ability to induce microvascular permeability, hence it is also called vascular permeability factor (VPF). VEGF-A has subsequently been shown to induce a number of biological processes including the mobilization of intracellular calcium, the induction of plasminogen activator and plasminogen activator inhibitor-1 synthesis, promotion of monocyte migration in vitro, induction of antiapoptotic protein expression in human endothelial cells, induction of fenestrations in endothelial cells, promotion of cell adhesion molecule expression in endothelial cells and induction of nitric oxide mediated vasodilation and hypotension [Ferrara, J Mol Med 77: 527-543 (1999); Neufeld et al., FASEB J 13: 9-22 (1999); Zachary, Intl J Biochem Cell Bio 30: 1169-1174 (1998)].

VEGF-A is a secreted, disulfide-linked homodimeric glycoprotein composed of 23 kD subunits. Five human VEGF-A isoforms of 121, 145, 165, 189 or 206 amino acids in length ($VEGF_{121-206}$), encoded by distinct mRNA splice variants, have been described, all of which are capable of stimulating mitogenesis in endothelial cells. However, each isoform differs in biological activity, receptor

specificity, and affinity for cell surface- and extracellular matrix-associated heparan-sulfate proteoglycans, which behave as low affinity receptors for VEGF-A. $VEGF_{121}$ does not bind to either heparin or heparan-sulfate; $VEGF_{145}$ and $VEGF_{165}$ (GenBank Acc. No. M32977) are both capable of binding to heparin; and $VEGF_{189}$ and $VEGF_{206}$ show the strongest affinity for heparin and heparan-sulfates. $VEGF_{121}$, $VEGF_{145}$, and $VEGF_{165}$ are secreted in a soluble form, although most of $VEGF_{165}$ is confined to cell surface and extracellular matrix proteoglycans, whereas $VEGF_{189}$ and $VEGF_{206}$ remain associated with extracellular matrix. Both $VEGF_{189}$ and $VEGF_{206}$ can be released by treatment with heparin or heparinase, indicating that these isoforms are bound to extracellular matrix via proteoglycans. Cell-bound $VEGF_{189}$ can also be cleaved by proteases such as plasmin, resulting in release of an active soluble $VEGF_{110}$. Most tissues that express VEGF are observed to express several VEGF isoforms simultaneously, although $VEGF_{121}$ and $VEGF_{165}$ are the predominant forms, whereas $VEGF_{206}$ is rarely detected [Ferrara, J Mol Med 77:527-543 (1999)]. $VEGF_{145}$ differs in that it is primarily expressed in cells derived from reproductive organs [Neufeld et al., FASEB J 13:9-22 (1999)].

The pattern of VEGF-A expression suggests its involvement in the development and maintenance of the normal vascular system, and in angiogenesis associated with tumor growth and other pathological conditions such as rheumatoid arthritis. VEGF-A is expressed in embryonic tissues associated with the developing vascular system, and is secreted by numerous tumor cell lines. Analysis of mice in which VEGF-A was knocked out by targeted gene disruption indicate that VEGF-A is critical for survival, and that the development of the cardiovascular system is highly sensitive to VEGF-A concentration gradients. Mice lacking a single copy of VEGF-A die between day 11 and 12 of gestation. These embryos show impaired growth and several developmental abnormalities including defects in the developing cardiovasculature. VEGF-A is also required post-natally for growth, organ development, regulation of growth plate morphogenesis and endochondral bone formation. The requirement for VEGF-A decreases with age, especially after the fourth postnatal week. In mature animals, VEGF-A is required primarily for active angiogenesis in processes such as wound healing and the development of the corpus luteum. [Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)]. VEGF-A expression is influenced primarily by hypoxia and a number of

hormones and cytokines including epidermal growth factor (EGF), TGF-ß, and various interleukins. Regulation occurs transcriptionally and also post-transcriptionally such as by increased mRNA stability [Ferrara, J Mol Med 77:527-543 (1999)].

PlGF, a second member of the VEGF subfamily, is generally a poor stimulator of angiogenesis and endothelial cell proliferation in comparison to VEGF-A, and the in vivo role of PlGF is not well understood. Three isoforms of PlGF produced by alternative mRNA splicing have been described [Hauser et al., Growth Factors 9:259-268 (1993); Maglione et al., Oncogene 8:925-931 (1993)]. PlGF forms both disulfide-linked homodimers and heterodimers with VEGF-A. The PlGF-VEGF-A heterodimers are more effective at inducing endothelial cell proliferation and angiogenesis than PlGF homodimers. PlGF is primarily expressed in the placenta, and is also co-expressed with VEGF-A during early embryogenesis in the trophoblastic giant cells of the parietal yolk sac [Stacker and Achen, Growth Factors 17:1-11 (1999)].

VEGF-B, described in detail in International Patent Publication No. WO 96/26736 and U.S. Patents 5,840,693 and 5,607,918, incorporated herein by reference, shares approximately 44% amino acid identity with VEGF-A. Although the biological functions of VEGF-B in vivo remain incompletely understood, it has been shown to have angiogenic properties, and may also be involved in cell adhesion and migration, and in regulating the degradation of extracellular matrix. It is expressed as two isoforms of 167 and 186 amino acid residues generated by alternative splicing. VEGF-B_{167} is associated with the cell surface or extracellular matrix via a heparin-binding domain, whereas VEGF-B_{186} is secreted. Both VEGF-B_{167} and VEGF-B_{186} can form disulfide-linked homodimers or heterodimers with VEGF-A. The association to the cell surface of $VEGF_{165}$-VEGF-B_{167} heterodimers appears to be determined by the VEGF-B component, suggesting that heterodimerization may be important for sequestering VEGF-A. VEGF-B is expressed primarily in embryonic and adult cardiac and skeletal muscle tissues [Joukov et al., J Cell Physiol 173:211-215 (1997); Stacker and Achen, Growth Factors 17:1-11 (1999)]. Mice lacking VEGF-B survive but have smaller hearts, dysfunctional coronary vasculature, and exhibit impaired recovery from cardiac ischemia [Bellomo et al., Circ Res 2000;E29-E35].

A fourth member of the VEGF subfamily, VEGF-C, comprises a VHD that is approximately 30% identical at the amino acid level to VEGF-A. VEGF-C is originally expressed as a larger precursor protein, prepro-VEGF-C, having extensive amino- and carboxy-terminal peptide sequences flanking the VHD, with the C-terminal peptide containing tandemly repeated cysteine residues in a motif typical of Balbiani ring 3 protein. Prepro-VEGF-C undergoes extensive proteolytic maturation involving the successive cleavage of a signal peptide, the C-terminal pro-peptide, and the N-terminal pro-peptide. Secreted VEGF-C protein consists of a non-covalently-linked homodimer, in which each monomer contains the VHD. The intermediate forms of VEGF-C produced by partial proteolytic processing show increasing affinity for the VEGFR-3 receptor, and the mature protein is also able to bind to the VEGFR-2 receptor. [Joukov et al., EMBO J., 16:(13):3898-3911 (1997).] It has also been demonstrated that a mutant VEGF-C, in which a single cysteine at position 156 is either substituted by another amino acid or deleted, loses the ability to bind VEGFR-2 but remains capable of binding and activating VEGFR-3 [U.S. Patent 6,130,071 and International Patent Publication No. WO 98/33917]. In mouse embryos, VEGF-C mRNA is expressed primarily in the allantois, jugular area, and the metanephros. [Joukov et al., J Cell Physiol 173:211-215 (1997)]. VEGF-C is involved in the regulation of lymphatic angiogenesis: when VEGF-C was overexpressed in the skin of transgenic mice, a hyperplastic lymphatic vessel network was observed, suggesting that VEGF-C induces lymphatic growth [Jeltsch et al., Science, 276:1423-1425 (1997)]. Continued expression of VEGF-C in the adult also indicates a role in maintenance of differentiated lymphatic endothelium [Ferrara, J Mol Med 77:527-543 (1999)]. VEGF-C also shows angiogenic properties: it can stimulate migration of bovine capillary endothelial (BCE) cells in collagen and promote growth of human endothelial cells [see, e.g., U.S. Patent 6,245,530; U.S. Patent 6,221,839; and International Patent Publication No. WO 98/33917, incorporated herein by reference].

The prepro-VEGF-C polypeptide is processed in multiple stages to produce a mature and most active VEGF-C polypeptide of about 21-23 kD (as assessed by SDS-PAGE under reducing conditions). Such processing includes cleavage of a signal peptide (SEQ ID NO: 24, residues 1-31); cleavage of a carboxyl-terminal peptide (corresponding approximately to amino acids 228-419 of SEQ ID NO: 24 and having a pattern of spaced cysteine residues reminiscent of a Balbiani

ring 3 protein (BR3P) sequence [Dignam et al., Gene, 88:133-40 (1990); Paulsson et al., J. Mol. Biol., 211:331-49 (1990)]) to produce a partially-processed form of about 29 kD; and cleavage (apparently extracellularly) of an amino-terminal peptide (corresponding approximately to amino acids 32-103 of SEQ ID NO: 24) to produced a fully-processed mature form of about 21-23 kD. Experimental evidence demonstrates that partially-processed forms of VEGF-C (e.g., the 29 kD form) are able to bind the Flt4 (VEGFR-3) receptor, whereas high affinity binding to VEGFR-2 occurs only with the fully processed forms of VEGF-C. It appears that VEGF-C polypeptides naturally associate as non-disulfide linked dimers.

Moreover, it has been demonstrated that amino acids 103-227 of SEQ ID NO: 24 are not all critical for maintaining VEGF-C functions. A polypeptide consisting of amino acids 113-213 (and lacking residues 103-112 and 214-227) of SEQ ID NO: 24 retains the ability to bind and stimulate VEGF-C receptors, and it is expected that a polypeptide spanning from about residue 131 to about residue 211 will retain VEGF-C biological activity. The cysteine residue at position 156 has been shown to be important for VEGFR-2 binding ability. However, VEGF-C ΔC156 polypeptides (i.e., analogs that lack this cysteine due to deletion or substitution) remain potent activators of VEGFR-3. The cysteine at position 165 of SEQ ID NO: 24 is essential for binding either receptor, whereas analogs lacking the cysteines at positions 83 or 137 compete with native VEGF-C for binding with both receptors and stimulate both receptors.

VEGF-D is structurally and functionally most closely related to VEGF-C [see U.S. Patent 6,235,713 and International Patent Publ. No. WO 98/07832, incorporated herein by reference]. Like VEGF-C, VEGF-D is initially expressed as a prepro-peptide that undergoes N-terminal and C-terminal proteolytic processing, and forms non-covalently linked dimers. VEGF-D stimulates mitogenic responses in endothelial cells in vitro. During embryogenesis, VEGF-D is expressed in a complex temporal and spatial pattern, and its expression persists in the heart, lung, and skeletal muscles in adults. Isolation of a biologically active fragment of VEGF-D designated VEGF-DΔNΔC, is described in International Patent Publication No. WO 98/07832, incorporated herein by reference. VEGF-DΔNΔC consists of amino acid residues 93 to 201 of VEGF-D (SEQ ID NO: 26) optionally linked to the affinity tag peptide FLAG®, or other sequences.

The prepro-VEGF-D polypeptide has a putative signal peptide of 21 amino acids and is apparently proteolytically processed in a manner analogous to the processing of prepro-VEGF-C. A "recombinantly matured" VEGF-D lacking residues 1-92 and 202-354 of SEQ ID NO: 26 retains the ability to activate receptors VEGFR-2 and VEGFR-3, and appears to associate as non-covalently linked dimers. Thus, preferred VEGF-D polynucleotides include those polynucleotides that comprise a nucleotide sequence encoding amino acids 93-201 of SEQ ID NO: 26. The guidance provided above for introducing function-preserving modifications into VEGF-C polypeptides is also suitable for introducing function-preserving modifications into VEGF-D polypeptides.

Four additional members of the VEGF subfamily have been identified in poxviruses, which infect humans, sheep and goats. The orf virus-encoded VEGF-E and NZ2 VEGF are potent mitogens and permeability enhancing factors. Both show approximately 25% amino acid identity to mammalian VEGF-A, and are expressed as disulfide-linked homodimers. Infection by these viruses is characterized by pustular dermititis which may involve endothelial cell proliferation and vascular permeability induced by these viral VEGF proteins. [Ferrara, J Mol Med 77:527-543 (1999); Stacker and Achen, Growth Factors 17:1-11 (1999)]. VEGF-like proteins have also been identified from two additional strains of the orf virus, D1701 [GenBank Acc. No. AF106020; described in Meyer et al., EMBO J 18:363-374 (1999)] and NZ10 [described in International Patent Application PCT/US99/25869, incorporated herein by reference]. These viral VEGF-like proteins have been shown to bind VEGFR-2 present on host endothelium, and this binding is important for development of infection and viral induction of angiogenesis [Meyer et al., EMBO J 18:363-374 (1999); International Patent Application PCT/US99/25869].

PDGF/VEGF Receptors

Seven cell surface receptors that interact with PDGF/VEGF family members have been identified. These include PDGFR-α (see e.g., GenBank Acc. No. NM006206) , PDGFR-β (see e.g., GenBank Acc. No. NM002609), VEGFR-1/Flt-1 (fms-like tyrosine kinase-1; GenBank Acc. No. X51602; De Vries et al., Science 255:989-991 (1992)); VEGFR-2/KDR/Flk-1 (kinase insert domain containing receptor/fetal liver kinase-1; GenBank Acc. Nos. X59397 (Flk-1) and L04947 (KDR); Terman et al., Biochem Biophys Res Comm 187:1579-1586 (1992); Matthews et al.,

Proc Natl Acad Sci USA 88:9026-9030 (1991)); VEGFR-3/Flt4 (fms-like tyrosine kinase 4; U.S. Patent Nos. 5,776,755 and GenBank Acc. No. X68203 and S66407; Pajusola et al., Oncogene 9:3545-3555 (1994)), neuropilin-1 (Gen Bank Acc. No. NM003873), and neuropilin-2 (Gen Bank Acc. No. NM003872). The two PDGF receptors mediate signaling of PDGFs as described above. VEGF121, VEGF165, VEGF-B, PlGF-1 and PlGF-2 bind VEGF-R1; VEGF121, VEGF145, VEGF165, VEGF-C, VEGF-D, VEGF-E, and NZ2 VEGF bind VEGF-R2; VEGF-C and VEGF-D bind VEGFR-3; VEGF165, VEGF-B, PlGF-2, and NZ2 VEGF bind neuropilin-1; and VEGF165, and VEGF145 bind neuropilin-2.[Neufeld et al., FASEB J 13:9-22 (1999); Stacker and Achen, Growth Factors 17:1-11 (1999); Ortega et al., Fron Biosci 4:141-152 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998); Petrova et al., Exp Cell Res 253:117-130 (1999); Gluzman-Poltorak et al., J. Biol. Chem. 275:18040-45 (2000)].

The PDGF receptors are protein tyrosine kinase receptors (PTKs) that contain five immunoglobulin-like loops in their extracellular domains. VEGFR-1, VEGFR-2, and VEGFR-3 comprise a subgroup of the PDGF subfamily of PTKs, distinguished by the presence of seven Ig domains in their extracellular domain and a split kinase domain in the cytoplasmic region. Both neuropilin-1 and neuropilin-2 are non-PTK VEGF receptors, with short cytoplasmic tails not currently known to possess downstream signaling capacity.

Several of the VEGF receptors are expressed as more than one isoform. A soluble isoform of VEGFR-1 lacking the seventh Ig-like loop, transmembrane domain, and the cytoplasmic region is expressed in human umbilical vein endothelial cells. This VEGFR-1 isoform binds VEGF-A with high affinity and is capable of preventing VEGF-A-induced mitogenic responses [Ferrara, J Mol Med 77:527-543 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)]. A C-terminal truncated from of VEGFR-2 has also been reported [Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)]. In humans, there are two isoforms of the VEGFR-3 protein which differ in the length of their C-terminal ends. Studies suggest that the longer isoform is responsible for most of the biological properties of VEGFR-3.

The expression of VEGFR-1 occurs mainly in vascular endothelial cells, although some may be present on monocytes, trophoblast cells, and renal mesangial cells [Neufeld et al., FASEB J 13:9-22 (1999)]. High levels of VEGFR-1

mRNA are also detected in adult organs, suggesting that VEGFR-1 has a function in quiescent endothelium of mature vessels not related to cell growth. VEGFR-1 -/- mice die in utero between day 8.5 and 9.5. Although endothelial cells developed in these animals, the formation of functional blood vessels was severely impaired, suggesting that VEGFR-1 may be involved in cell-cell or cell-matrix interactions associated with cell migration. Recently, it has been demonstrated that mice expressing a mutated VEGFR-1 in which only the tyrosine kinase domain was missing show normal angiogenesis and survival, suggesting that the signaling capability of VEGFR-1 is not essential. [Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)].

VEGFR-2 expression is similar to that of VEGFR-1 in that it is broadly expressed in the vascular endothelium, but it is also present in hematopoietic stem cells, megakaryocytes, and retinal progenitor cells [Neufeld et al., FASEB J 13:9-22 (1999)]. Although the expression pattern of VEGFR-1 and VEGFR-2 overlap extensively, evidence suggests that, in most cell types, VEGFR-2 is the major receptor through which most of the VEGFs exert their biological activities. Examination of mouse embryos deficient in VEGFR-2 further indicate that this receptor is required for both endothelial cell differentiation and the development of hematopoietic cells [Joukov et al., J Cell Physiol 173:211-215 (1997)].

VEGFR-3 is expressed broadly in endothelial cells during early embryogenesis. During later stages of development, the expression of VEGFR-3 becomes restricted to developing lymphatic vessels [Kaipainen, A., et al., Proc. Natl. Acad. Sci. USA, 92: 3566-3570 (1995)]. In adults, the lymphatic endothelia and some high endothelial venules express VEGFR-3, and increased expression occurs in lymphatic sinuses in metastatic lymph nodes and in lymphangioma. VEGFR-3 is also expressed in a subset of CD34+ hematopoietic cells which may mediate the myelopoietic activity of VEGF-C demonstrated by overexpression studies [WO 98/33917]. Targeted disruption of the VEGFR-3 gene in mouse embryos leads to failure of the remodeling of the primary vascular network, and death after embryonic day 9.5 [Dumont et al., Science, 282: 946-949 (1998)]. These studies suggest an essential role for VEGFR-3 in the development of the embryonic vasculature, and also during lymphangiogenesis.

Structural analyses of the VEGF receptors indicate that the VEGF-A binding site on VEGFR-1 and VEGFR-2 is located in the second and third Ig-like loops. Similarly, the VEGF-C and VEGF-D binding sites on VEGFR-2 and VEGFR-3 are also contained within the second Ig-loop [Taipale et al., Curr Top Microbiol Immunol 237:85-96 (1999)]. The second Ig-like loop also confers ligand specificity as shown by domain swapping experiments [Ferrara, J Mol Med 77:527-543 (1999)]. Receptor-ligand studies indicate that dimers formed by the VEGF family proteins are capable of binding two VEGF receptor molecules, thereby dimerizing VEGF receptors. The fourth Ig-like loop on VEGFR-1, and also possibly on VEGFR-2, acts as the receptor dimerization domain that links two receptor molecules upon binding of the receptors to a ligand dimer [Ferrara, J Mol Med 77:527-543 (1999)]. Although the regions of VEGF-A that bind VEGFR-1 and VEGFR-2 overlap to a large extent, studies have revealed two separate domains within VEGF-A that interact with either VEGFR-1 or VEGFR-2, as well as specific amino acid residues within these domains that are critical for ligand-receptor interactions. Mutations within either VEGF receptor-specific domain that specifically prevent binding to one particular VEGF receptor have also been recovered [Neufeld et al., FASEB J 13:9-22 (1999)].

VEGFR-1 and VEGFR-2 are structurally similar, share common ligands (VEGF121 and VEGF165), and exhibit similar expression patterns during development. However, the signals mediated through VEGFR-1 and VEGFR-2 by the same ligand appear to be slightly different. VEGFR-2 has been shown to undergo autophosphorylation in response to VEGF-A, but phosphorylation of VEGFR-1 under identical conditions was barely detectable. VEGFR-2 mediated signals cause striking changes in the morphology, actin reorganization, and membrane ruffling of porcine aortic endothelial cells recombinantly overexpressing this receptor. In these cells, VEGFR-2 also mediated ligand-induced chemotaxis and mitogenicity; whereas VEGFR-1-transfected cells lacked mitogenic responses to VEGF-A. Mutations in VEGF-A that disrupt binding to VEGFR-2 fail to induce proliferation of endothelial cells, whereas VEGF-A mutants that are deficient in binding VEGFR-1 are still capable of promoting endothelial proliferation. Similarly, VEGF stimulation of cells expressing only VEGFR-2 leads to a mitogenic response whereas comparable stimulation of cells expressing only VEGFR-1 also results in cell migration, but does not induce cell proliferation. In addition, phosphoproteins co-precipitating with

VEGFR-1 and VEGFR-2 are distinct, suggesting that different signaling molecules interact with receptor-specific intracellular sequences.

The emerging hypothesis is that the primary function of VEGFR-1 in angiogenesis may be to negatively regulate the activity of VEGF-A by binding it and thus preventing its interaction with VEGFR-2, whereas VEGFR-2 is thought to be the main transducer of VEGF-A signals in endothelial cells. In support of this hypothesis, mice deficient in VEGFR-1 die as embryos while mice expressing a VEGFR-1 receptor capable of binding VEGF-A but lacking the tyrosine kinase domain survive and do not exhibit abnormal embryonic development or angiogenesis. In addition, analyses of VEGF-A mutants that bind only VEGFR-2 show that they retain the ability to induce mitogenic responses in endothelial cells. However, VEGF-mediated migration of monocytes is dependent on VEGFR-1, indicating that signaling through this receptor is important for at least one biological function. In addition, the ability of VEGF-A to prevent the maturation of dendritic cells is also associated with VEGFR-1 signaling, suggesting that VEGFR-1 may function in cell types other than endothelial cells. [Ferrara, J Mol Med 77:527-543 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)].

With respect to the neuropilins or other polypeptides used to practice the invention, it will be understood that native sequences will usually be most preferred. By "native sequences" is meant sequences encoded by naturally occurring polynucleotides, including but not limited to prepro-peptides, pro-peptides, and partially and fully proteolytically processed polypeptides. As described above, many of the polypeptides have splice variants that exist, e.g., due to alternative RNA processing, and such splice variants comprise native sequences. For purposes described herein, fragments of the forgoing that retain the binding properties of interest also shall be considered native sequences. Moreover, modifications can be made to most protein sequences without destroying the activity of interest of the protein, especially conservative amino acid substitutions, and proteins so modified are also suitable for practice of the invention. By "conservative amino acid substitution" is meant substitution of an amino acid with an amino acid having a side chain of a similar chemical character. Similar amino acids for making conservative substitutions include those having an acidic side chain (glutamic acid, aspartic acid); a basic side chain (arginine, lysine, histidine); a polar amide side chain (glutamine, asparagine); a

hydrophobic, aliphatic side chain (leucine, isoleucine, valine, alanine, glycine); an aromatic side chain (phenylalanine, tryptophan, tyrosine); a small side chain (glycine, alanine, serine, threonine, methionine); or an aliphatic hydroxyl side chain (serine, threonine).

Moreover, deletion and addition of amino acids is often possible without destroying a desired activity. With respect to the present invention, where binding activity is of particular interest and the ability of molecules to activate or inhibit receptor tyrosine kinases upon binding is of special interest, binding assays and tyrosine phophorylation assays are available to determine whether a particular ligand or ligand variant (a) binds and (b) stimulates or inhibits RTK activity.

Two manners for defining genera of polypeptide variants include percent amino acid identity to a native polypeptide (e.g., 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity preferred), or the ability of encoding-polynucleotides to hybridize to each other under specified conditions. One exemplary set of conditions is as follows: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM Na•PO4, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes. Formula for calculating equivalent hybridization conditions and/or selecting other conditions to achieve a desired level of stringency are well known. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel, et al. (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, et al., (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

B. Gene Therapy

While much of the application, including the examples, are written in the context of protein-protein interactions and protein administration, it should be clear that genetic manipulations to achieve modulation of protein expression or activity is specifically contemplated. For example, where administration of proteins is contemplated, administration of a gene therapy vector to cause the protein of interest to be produced in vivo also is contemplated. Where inhibition of proteins is

contemplated (e.g., through use of antibodies or small molecule inhibitors), inhibition of protein expression in vivo by genetic techniques, such as knock-out techniques or anti-sense therapy, is contemplated.

Any suitable vector may be used to introduce a transgene of interest into an animal. Exemplary vectors that have been described in the literature include replication-deficient retroviral vectors, including but not limited to lentivirus vectors [Kim et al., J. Virol., 72(1): 811-816 (1998); Kingsman & Johnson, Scrip Magazine, October, 1998, pp. 43-46.]; adeno-associated viral vectors [Gnatenko et al., J. Investig. Med., 45: 87-98 (1997)]; adenoviral vectors [See, e.g., U.S. Patent No. 5,792,453; Quantin et al., Proc. Natl. Acad. Sci. USA, 89: 2581-2584 (1992); Stratford-Perricadet et al., J. Clin. Invest., 90: 626-630 (1992); and Rosenfeld et al., Cell, 68: 143-155 (1992)]; Lipofectin-mediated gene transfer (BRL); liposomal vectors [See, e.g., U.S. Patent No. 5,631,237 (Liposomes comprising Sendai virus proteins)] ; and combinations thereof. All of the foregoing documents are incorporated herein by reference in the entirety. Replication-deficient adenoviral vectors and adeno-associated viral vectors constitute preferred embodiments.

In embodiments employing a viral vector, preferred polynucleotides include a suitable promoter and polyadenylation sequence to promote expression in the target tissue of interest. For many applications of the present invention, suitable promoters/enhancers for mammalian cell expression include, e.g., cytomegalovirus promoter/enhancer [Lehner et al., J. Clin. Microbiol., 29:2494-2502 (1991); Boshart et al., Cell, 41:521-530 (1985)]; Rous sarcoma virus promoter [Davis et al., Hum. Gene Ther., 4:151 (1993)]; or simian virus 40 promoter.

Anti-sense polynucleotides are polynucleotides which recognize and hybridize to polynucleotides encoding a protein of interest and can therefore inhibit transription or translation of the protein. Full length and fragment anti-sense polynucleotides may be employed. Commercial software is available to optimize antisense sequence selection and also to compare selected sequences to known genomic sequences to help ensure uniqueness/specificity for a chosen gene. Such uniqueness can be further confirmed by hybridization analyses. Antisense nucleic acids (preferably 10 to 20 base pair oligonucleotides) are introduced into cells (e.g., by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the target nucleotide sequence in the cell and prevents

transcription or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by poly-L-lysine, transferrin polylysine, or cholesterol moieneuropilins at their 5' end.

Genetic control can also be achieved through the design of novel transcription factors for modulating expression of the gene of interest in native cells and animals. For example, the Cys2-His2 zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries [Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763; Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30; Greisman and Pabo (1997) Science 275:657-61; Choo et al., (1997) J Mol Biol 273:525-32]. Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence [Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763]. The artificial zinc finger repeats, designed based on target sequences, are fused to activation or repression domains to promote or suppress gene expression [Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30]. Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors [Kim et al., (1997) Proc Natl Acad Sci USA 94:3616-3620]. Such proteins, and polynucleotides that encode them, have utility for modulating expression in vivo in both native cells, animals and humans. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences

for use in therapeutics as alternatives to antisense or catalytic RNA methods [McColl et al., (1999) Proc Natl Acad Sci USA 96:9521-6; Wu et al., (1995) Proc Natl Acad Sci USA 92:344-348].

C. Antibodies

Antibodies are useful for modulating Neuropilin-VEGF-C interactions due to the ability to easily generate antibodies with relative specificity, and due to the continued improvements in technologies for adopting antibodies to human therapy. Thus, the invention contemplates use of antibodies (e.g., monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for polypeptides of interest to the invention, especially neuropilins, VEGF receptors, and VEGF-C and VEGF-D proteins. Preferred antibodies are human antibodies which are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab′, F(ab′)2, and Fv, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the invention recognize and bind the polypeptide of interest exclusively (i.e., able to distinguish the polypeptides of interest from other known polypeptides of the same family, by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between family members). It will be understood that specific antibodies may also interact with other proteins (for example, S. aureus protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor , NY (1988), Chapter 6. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for NRP-2, the other one is for an NRP-2 binding partner, and preferably for a cell-surface protein or receptor or receptor subunit, such as VEGFR-3.

In one embodiment, a bispecific antibody which binds to both NRP-2 and VEGFR-3 is used to modulate the growth, migration or proliferation of cells that results from the interaction of VEGF-C with VEGFR-3. For example, the bispecific antibody is administered to an individual having tumors characterized by lymphatic metastasis or other types of tumors expressing both VEGF-C and VEGFR-3, and NRP-2. The bisepcific antibody which binds both NRP-2 and VEGFR-3 blocks the binding of VEGF-C to VEGFR-3, thereby interfereing with VEGF-C mediated lymphangiogenesis and slowing the progression of tumor metastatsis. In another embodiment, the same procedure is carried out with a bispecific antibody which binds to NRP-2 and VEGF-C, wherein administration of said antibody sequesters soluble VEGF-C and prevents its binding to VEGFR-3, effectively acting as an inhibitor of VEGF-C mediated signaling through VEGFR-3.

Bispecific antibodies are produced, isolated, and tested using standard procedures that have been described in the literature. See, e.g., Pluckthun & Pack, Immunotechnology, 3:83-105 (1997); Carter et al., J. Hematotherapy, 4: 463-470 (1995); Renner & Pfreundschuh, Immunological Reviews, 1995, No. 145, pp. 179-209; Pfreundschuh U.S. Patent No. 5,643,759; Segal et al., J. Hematotherapy, 4: 377-382 (1995); Segal et al., Immunobiology, 185: 390-402 (1992); and Bolhuis et al., Cancer Immunol. Immunother., 34: 1-8 (1991), all of which are incorporated herein by reference in their entireties.

The term "bispecific antibody" refers to a single, divalent antibody which has two different antigen binding sites (variable regions). As described below, the bispecific binding agents are generally made of antibodies, antibody fragments, or analogs of antibodies containing at least one complementarity determining region derived from an antibody variable region. These may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. Current Opinion Biotechnol. 4, 446-449 (1993)), e.g. prepared chemically, using hybrid hybridomas, via linking the coding sequence of such a bispecific antibody into

a vector and producing the recombinant peptide or by phage display. The bispecific antibodies may also be any bispecific antibody fragments.

In one method, bispecific antibodies fragments are constructed by converting whole antibodies into (monospecific) $F(ab')_2$ molecules by proteolysis, splitting these fragments into the Fab' molecules and recombine Fab' molecules with different specificity to bispecific $F(ab')_2$ molecules (see, for example, U.S. Patent 5,798,229).

A bispecific antibody can be generated by enzymatic conversion of two different monoclonal antibodies, each comprising two identical L (light chain)-H (heavy chain) half molecules and linked by one or more disulfide bonds, into two F(ab')2 molecules, splitting each F(ab')2 molecule under reducing conditions into the Fab' thiols, derivatizing one of these Fab' molecules of each antibody with a thiol activating agent and combining an activated Fab' molecule bearing NRP-2 specificity with a non-activated Fab' molecule bearing an NRP-2 binding partner specificity or vice versa in order to obtain the desired bispecific antibody F(ab')2 fragment.

As enzymes suitable for the conversion of an antibody into its F(ab')2 molecules, pepsin and papain may be used. In some cases, trypsin or bromelin are suitable. The conversion of the disulfide bonds into the free SH-groups (Fab' molecules) may be performed by reducing compounds, such as dithiothreitol (DTT), mercaptoethanol, and mercaptoethylamine. Thiol activating agents according to the invention which prevent the recombination of the thiol half-molecules, are 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 2,2'-dipyridinedisulfide, 4,4'-dipyridinedisulfide or tetrathionate/sodium sulfite (see also Raso et al., Cancer Res., 42:457 (1982), and references incorporated therein).

The treatment with the thiol-activating agent is generally performed only with one of the two Fab' fragments. Principally, it makes no difference which one of the two Fab' molecules is converted into the activated Fab' fragment (e.g., Fab'-TNB). Generally, however, the Fab' fragment being more labile is modified with the thiol-activating agent. In the present case, the fragments bearing the anti-tumor specificity are slightly more labile, and, therefore, preferably used in the process. The conjugation of the activated Fab' derivative with the free hinge-SH groups of the second Fab' molecule to generate the bivalent F(ab') 2 antibody occurs spontaneously

at temperatures between 0° and 30° C. The yield of purified F(ab').sub.2 antibody is 20-40% (starting from the whole antibodies).

Another method for producing bispecific antibodies is by the fusion of two hybridomas to form a hybrid hybridoma. As used herein, the term "hybrid hybridoma" is used to describe the productive fusion of two B cell hybridomas. Using now standard techniques, two antibody producing hybridomas are fused to give daughter cells, and those cells that have maintained the expression of both sets of clonotype immunoglobulin genes are then selected.

To identify the bispecific antibody standard methods such as ELISA are used wherein the wells of microtiter plates are coated with a reagent that specifically interacts with one of the parent hybridoma antibodies and that lacks cross-reactivity with both antibodies. In addition, FACS, immunofluorescence staining, idiotype specific antibodies, antigen binding competition assays, and other methods common in the art of antibody characterization may be used in conjunction with the present invention to identify preferred hybrid hybridomas.

Bispecific molecules of this invention can also be prepared by conjugating a gene encoding a binding specificity for NRP-2 to a gene encoding at least the binding region of an antibody chain which recognizes a binding partner of NRP-2 such as VEGF-C or VEGFR-3. This construct is transfected into a host cell (such as a myeloma) which constitutively expresses the corresponding heavy or light chain, thereby enabling the reconstitution of a bispecific, single-chain antibody, two-chain antibody (or single chain or two-chain fragment thereof such as Fab) having a binding specificity for NRP-2 and for a NRP-2 binding partner. Construction and cloning of such a gene construct can be performed by standard procedures.

Bispecific antibodies are also generated via phage display screening methods using the so-called hierarchical dual combinatorial approach as disclosed in WO 92/01047 in which an individual colony containing either an H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H) and the resulting two-chain specific binding member is selected in accordance with phage display techniques such as those described therein. This technique is also disclosed in Marks et al, (Bio/Technology, 1992, 10:779-783).

The bispecific antibody fragments of the invention can be administered to human patients for therapy. Thus, in one embodiment the bispecific antibody is provided with a pharmaceutical formulation comprising as active ingredient at least one bispecific antibody fragment as defined above, associated with one or more pharmaceutically acceptable carrier, excipient or diluent. In another embodiment, the compound further comprises an anti-neoplastic or cytotoxic agent conjugated to the bispecific antibody.

Recombinant antibody fragments, e.g. scFvs, can also be engineered to assemble into stable multimeric oligomers of high binding avidity and specificity to different target antigens. Such diabodies (dimers), triabodies (trimers) or tetrabodies (tetramers) are well known within the art and have been described in the literature, see e.g. Kortt et al., Biomol Eng. 2001 Oct 15;18(3):95-108 and Todorovska et al., J Immunol Methods. 2001 Feb 1;248(1-2):47-66.

Non-human antibodies may be humanized by any methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

D. Dosing

Some methods of the invention include a step of polypeptide administration to a human or animal. Polypeptides may be administered in any suitable manner using an appropriate pharmaceutically-acceptable vehicle, e.g., a pharmaceutically-acceptable diluent, adjuvant, excipient or carrier. The composition to be administered according to methods of the invention preferably comprises (in addition to the polynucleotide or vector) a pharmaceutically-acceptable carrier solution such as water, saline, phosphate-buffered saline, glucose, or other carriers conventionally used to deliver therapeutics or imaging agents.

The "administering" that is performed according to the present invention may be performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian subject, including but not limited to injections (e.g., intravenous, intramuscular, subcutaneous, or catheter); oral ingestion; intranasal or topical administration; and the like. For some cardiovascular disesases a preferred route of administration is intravascular, such as by intravenous,

intra-arterial, or intracoronary arterial injection. In one embodiment, administering the composition is performed at the site of a lesion or affected tissue needing treatment by direct injection into the lesion site or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally. For example, biodegradeable microspheres or capsules or other biodegradeable polymer configurations capable of sustained delivery of a composition (e.g., a soluble polypeptide, antibody, or small molecule) can be included in the formulations of the invention implanted near the lesion.

The therapeutic composition may be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of several hours. In certain cases it may be beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, daily, weekly or monthly.

Polypeptides for administration may be formulated with uptake or absorption enhancers to increase their efficacy. Such enhancer include for example, salicylate, glycocholate/linoleate, glycholate, aprotinin, bacitracin, SDS caprate and the like. See, e.g., Fix (J. Pharm. Sci., 85(12) 1282-1285, 1996) and Oliyai and Stella (Ann. Rev. Pharmacol. Toxicol., 32:521-544, 1993).

The amounts of peptides in a given dosage will vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated. In exemplary treatments, it may be necessary to administer about 50mg/day, 75 mg/day, 100mg/day, 150mg/day, 200mg/day, 250 mg/day. These concentrations may be administered as a single dosage form or as multiple doses. Standard dose-response studies, first in animal models and then in clinical testing, reveal optimal dosages for particular disease states and patient populations.

It will also be apparent that dosing should be modified if traditional therapeutics are administered in combination with therapuetics of the invention. For example, treatment of cancer using traditional chemotherapeutic agents or radiation, in combination with methods of the invention, is contemplated.

E. Kits

As an additional aspect, the invention includes kits which comprise one or more compounds or compositions of the invention packaged in a manner which facilitates their use to practice methods of the invention. In a simplest embodiment, such a kit includes a compound or composition described herein as useful for practice of a method of the invention (e.g., polynucleotides or polypeptides for administration to a person or for use in screening assays), packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition to practice the method of the invention. Preferably, the compound or composition is packaged in a unit dosage form. The kit may further include a device suitable for administering the composition according to a preferred route of administration or for practicing a screening assay.

Additional aspects and details of the invention will be apparent from the following examples, which are intended to be illustrative rather than limiting.

EXAMPLE 1
VEGF-C ISOFORMS BIND TO NEUROPILIN-2 AND NEUROPILIN-1

The following experiments demonstrated that VEGF-C isoforms interact with the neuropilin family members, neuropilin-2 and neuropilin-1.

A. Materials

To investigate the binding of neuropilin-2 to VEGF-C the following constructs were either made or purchased from commercial sources:

a) Cloning of the NRP-2/IgG expression vector. The extracellular domain of hNRP-2 was cloned into the pIgplus vector in frame with the human IgG1 Fc tail as follows. Full-length NRP-2 cDNA (SEQ ID NO. 3) was assembled from several IMAGE Consortium cDNA Clones (Incyte Genomics) (Fig. 1A). The Image clones used are marked as 2A (GenBank Acc. No AA621145; Clone ID 1046499), 3 (AA931763; 1564852), 4 (AA127691; 490311), and 5 (AW296186; 2728688); these clones were confirmed by sequencing. Image clones 4 and 5 differ due to alternative splicing, coding for a17 and a22 isoforms, respectively. The BamHI-NotI fragment from the image clone 3 was first cloned into the pcDNA3.1z+ vector (Invitrogen), and fragments KpnI-BglII from clone 2A and BglII-BamHI from clone 3 were then added

to obtain the 5' region (bp 1-2188). NotI-BamHI fragments from clones 4 and 5 were separately transferred into the pIgplus vector, and the KpnI-NotI fragment from the pcDNA3.1z+ vector was then inserted to obtain the expression vector coding for the extracellular domain of the hNRP-2/IgG fusion protein (SEQ ID NO. 3, positions 1 to 2577). The NRP-2 inserts in the resulting vectors were sequenced. The Image clone 3 codes for one amino acid different from the GenBank Sequence (AAA 1804-1806 GAG | K602E). However, the amino acid sequence in the Image clone 3 is identical to the original sequence published by Chen et al. (Chen et al., Neuron, 19:547. 1997).

b) a VEGFR-3-Fc construct, in which an extracellular domain portion of VEGFR-3 comprising the first three immunoglobulin-like domains (SEQ ID NO. 32, amino acids 1 to 329) was fused to the Fc portion of human IgG1 [see Makinen et al., Nat Med., 7:199-205 (2001)]. Full length VEGFR-3 cDNA and amino acid sequences are set forth in SEQ. ID NOS: 31 and 32.

c) a NRP-1-Fc construct, in which an extracellular domain portion of murine NRP-1 (base pairs 248-2914 of SEQ. ID NO: 5) was fused to the Fc portion of human IgG1 (Makinen et al, J. Biol.Chem 274:21217-222. 1999); and

d) the expression vectors, in pREP7 backbone, encoding either VEGF165 (Genbank Accession No. M32997) or full-length VEGF-C (SEQ. ID NO:24), have been described recently (Olofsson et al., Proc. Natl. Acad. Sci. USA 93: 2576-81. 1996; and Joukov et al., EMBO J. 15: 290-298. 1996).

B. Co-immunoprecipitation of VEGF-C with NRP-2

The NRP-2, NRP-1, and VEGFR-3 pIgplus fusion constructs were transfected into 293T cells using the FUGENETM6 transfection reagent (Roche Molecular Biochemicals). The cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (Gibco BRL), glutamine, and antibiotics. The media was replaced 48 h after transfection by DMEM containing 0.2% BSA and collected after 20 h.

For growth factor production, 293EBNA cells were transfected with expression vectors coding for $VEGF_{165}$, prepro-VEGF-C, or empty vector (Mock). 36 h after transfection, the cells were first incubated in methionine and cysteine free MEM (Gibco BRL) for 45 min, metabolically labeled in the same medium

supplemented with 100 millicurie [mCi]/ml Pro-mix [35S] (Amersham) for 6-7 h (1 mCi=37 kBq) containing radiolabelled methionine and cysteine.

For immunoprecipitation controls, 1 ml of the labeled medium was incubated with either MAB 293 monoclonal anti-VEGF-Ab (R&D Systems), or rabbit antiserum 882 against VEGF-C (Joukov et al., EMBO J. 16:3898-3911. 1997) for 2 h, with rotation, at +4° C. Protein A-Sepharose (Pharmacia) was then added, and incubated overnight. The immunoprecipitates were washed two times with ice-cold PBS-0.5% Tween 20, heated in Laemmli sample buffer, and electrophoresed in 15% SDS PAGE. The gel was dried and exposed to Kodak Biomax MR film.

For binding experiments, the labeled supernatants from the Mock- or VEGF-C transfected cells were first immunoprecipitated with VEGF antibodies (R & D Systems) for depletion of endogenous VEGF. 4 ml of hNRP-2 a17-IgG or 1 ml of VEGFR-3-IgG or NRP-1-IgG fusion protein containing media were incubated with 1 ml of growth factor containing media (Mock, VEGF or VEGF-C) in binding buffer (0.5% BSA, 0.02% Tween 20) for 2 h, Protein A-Sepharose was added, and incubated overnight. The samples were then washed once with ice-cold binding buffer and three times with PBS and subjected to 15% SDS PAGE. The radiolabeled VEGF-C polypeptide was detected via chemiluminescence (ECL).

Results show that both the 29 kD and 21-23 kD isoforms of VEGF-C bind to NRP-2 while only the 29 kD form binds to NRP-1. VEGFR-3 binding to VEGF-C was used as a positive control for VEGF-C binding in the assay. It has been shown previously that heparin strongly increases VEGF binding to NRP-2 (Gluzman-Poltorak et al., J. Biol.Chem. 275: 18040-045. 2000). Addition of heparin to the assay mixture illustrates that $VEGF_{165}$ binding to NRP-2 is heparin dependent while $VEGF_{165}$ binding to NRP-1 is independent of heparin binding, and the presence of heparin has no effect on VEGF-C binding to any of its receptors.

C. Cell-based assay using cells that naturally express Neuropilin receptors.

The preceding experiment can be modified by substituting cells that naturally express a neuropilin receptor (especially NRP-2) for the transfected 293EBNA cells. Use of primary cultures of neuronal cells expressing neuropilin receptors is specifically contemplated, e.g., cultured cerebellar granule cells derived from embryos. Additionally, NRP-receptor-specific antibodies can be employed to

identify other cells (e.g., cells involved in the vasculature), such as human microvascular endothelial cells (HMVEC), human cutaneous fat pad microvascular cells (HUCEC) that express NRP receptors.

EXAMPLE 2
NEUROPILIN-2 INTERACTS WITH VEGFR-3

Recent results indicate that NRP-1 is a co-receptor for $VEGF_{165}$ binding, forming a complex with VEGFR-2, which results in enhanced $VEGF_{165}$ signaling through VEGFR-2, over $VEGF_{165}$ binding to VEGFR-2 alone, thereby enhancing the biological responses to this ligand (Soker et al., Cell 92: 735-45. 1998). A similar phenomenon may apply to VEGF-C signaling via possible VEGFR-3/NRP-2 receptor complexes.

A. Binding Assay

The NRP-2(a22) expression vector was cloned as described in Example 1 (Fig. 1B) with the addition of a detectable tag on the 3' end. For 3' end construction, the Not I-Bam HI fragment (clone 5) was then constructed by PCR, introducing the V5 tag (GKPIPNPLLGLDST) (SEQ ID NO:33) and a stop codon to the 3' terminus. To obtain the expression vector coding for the full-length hNRP-2(a22) protein, this 3' end was then transferred into the vector containing the 5' fragment. The resulting clone was referred to as V5 NRP-2.

To determine the interaction of VEGFR-3 with NRP-2, 10 cm plates of human embryonic kidney cells (293T or 293EBNA) were transfected with the V5 NRP-2 construct or VEGFR-3 using 6 µl of FUGENE TM6 (Roche Molecular Biochemicals, Indianapolis, Indiana) and 2 µg DNA. The cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (Gibco BRL), glutamine, and antibiotics. For Mock transfections, 2 µg of empty vector was used. For single receptor transfections, the VEGFR-3-myc/pcDNA3.1 (Karkkainen et al, Nat. Genet. 25:153-59. 2000) or NRP-2(a22)/pcDNA3.1z+and empty vector were used in a one to one ratio. The VEGFR-3/NRP-2 co-transfections were also made in a one to one ratio. After 24 h, the 293EBNA cells were starved overnight, and stimulated for 10 min using 300 ng/ml ΔNΔCVEGF-C (produced in *P. pastoris*; (Joukov et al. EMBOJ. 16: 3898-3911. 1997)). The cells were then washed twice with ice-cold PBS containing vanadate (100 µM) and PMSF (100 µM), and lysed in

dimerization lysis buffer (20 mM HEPES pH 7.5,150 mM NaCl,10%glycerol,1% Triton X-100,2 mM $MgCl_2$, 2 mM $CaCl_2$,10 µg/ml bovine serum albumin (BSA)) containing 2 mM vanadate,1 mM PMSF, 0.07 U/ml aprotinin, and 4 µg/ml leupeptin. The lysates were cleared by centrifugation for 10 min at 19,000g, and incubated with antibodies for VEGFR-3 (9d9F;(Jussila et al., Cancer Res. 58: 1599-1604. 1998)), or V5 (Invitrogen) for 5 h at +4 °C. The immunocomplexes were then incubated with protein A-Sepharose (Pharmacia) overnight at +4 °C, the immunoprecipitates were washed four times with dimerization lysis buffer without BSA, and the samples subjected to 7.5%SDS-PAGE in reducing conditions. The proteins were transferred to a Protran nitrocellulose filter (Schleicher & Schuell) using semi-dry transfer apparatus. After blocking with 5% non-fat milk powder in TBS-T buffer (10 mM Tris pH 7.5,150 mM NaCl, 0.1%Tween 20), the filters were incubated with the V5 antibodies, followed by HRP-conjugated rabbit-anti-mouse immunoglobulins (Dako), and visualized using enhanced chemiluminescence (ECL).

Co-immunoprecipitation of VEGFR-3 and NRP-2 constructs transfected into 293T cells demonstrates that NRP-2 interacts with VEGFR-3 when co-expressed in the same cell. Immunoprecipitation after the addition of VEGF-C to the cell culture media shows that the NRP-2/VEGFR-3 interaction is not dependent on the presence of the VEGF-C ligand, implying that these receptors may associate naturally in vivo without the presence of VEGF-C. This finding may have tremendous implications on the binding and activity of VEGF-C during angiogenesis. VEGF-C, an integral molecule in promoting growth and development of the lymphatic vasculature, is also highly involved in the metastasis of cancerous cells through the lymph system and apparently the neovascularization of at least some solid tumors (see International Patent Publication No. WO 00/21560). The novel interaction between neuropilins and VEGF-C provides for a means to specifically block this lymphatic growth into solid tumors by inhibiting lymphatic cell migration as a result of VEGF-C binding to VEGFR-3. Neuropilins-1 and-2 are the only VEGF receptors at the surface of some tumor cells, indicating the binding of VEGF to neuropilins is relevant to tumor growth (Soker et al, Cell 92: 735-45. 1998) and that VEGF-C binding to neuropilin-2 may be a means to specifically target tumor metastasis through the lymphatic system.

EXAMPLE 3
INHIBITION OF VEGF-C BINDING TO VEGFR-3 BY NEUROPILINS

The binding affinity between VEGF-C and neuropilin receptor molecules provides therapeutic indications for modulators of VEGF-C-induced VEGFR-3 receptor signaling, in order to modulate, i.e. stimulate or inhibit, VEGF-receptor-mediated biological processes. The following examples are designed to provide proof of this therapeutic concept.

A. *In vitro* cell-free assay

To demonstrate the inhibitory effects of neuropilin-1-Fc and neuropilin-2-Fc against VEGF-C stimulation, a label, e.g. a biotin molecule, is fused with the VEGF-C protein and first incubated with neuropilin-1-Fc, neuropilin-2-Fc, VEGFR-2 Fc or VEGFR-3-Fc at various molar ratios, and then applied on microtiter plates pre-coated with 1 microgram/ml of VEGFR-3 or VEGFR-2. After blocking with 1%BSA/PBS-T, fresh, labeled VEGF-C protein or the VEGF-C/receptor-Fc mixture above is applied on the microtiter plates overnight at 4 degrees Centigrade. Thereafter, the plates are washed with PBS-T, and 1:1000 of avidin-HRP will be added. Bound VEGF-C protein is detected by addition of the ABTS substrate (KPL). The bound labeled VEGF-C is analyzed in the presence and absence of the soluble neuropilins or soluble VEGFRs and the percent inhibition of binding assessed, as well as the effects the neuropilins have on binding to either VEGFR-2 or VEGFR-3 coated microtiter plates. In a related variation, this assay is carried out substituting VEGF-D for VEGF-C.

B. *In vitro* cell-based assay

VEGF-C is used as described above to contact cells that naturally or recombinantly express NRP-2 and VEGFR-3 receptors on their surface. By way of example, 293EBNA or 293T cells recombinantly modified to transiently or stably express neuropilins and VEGFR-3 as outlined above are employed. Several native endothelial cell types express both receptors and can also be employed, including but not limited to, human microvascular endothelial cells (HMEC) and human cutaneous fat pad microvascular cells (HUCEC).

For assessment of autophosphorylation of VEGFR-3, 293T or 293EBNA human embryonic kidney cells grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (GIBCO BRL), glutamine

and antibiotics, are transfected using the FUGENETM 6 transfection reagent (Roche Molecular Biochemicals) with plasmid DNAs encoding the receptor constructs (VEGFR-3 or VEGFR-3-myc tag and/or neuropilin-V5 tag,) or an empty pcDNA3.1z+ vector (Invitrogen). For stimulation assay, the 293EBNA cell monolayers are starved overnight (36 hours after transfection) in serum-free medium containing 0.2% BSA. The 293EBNA cells are then stimulated with 300 ng/ml recombinant DNDC VEGF-C (Joukov et al., EMBO J. 16:3898-3911. 1997) for 10 min at +37 °C, in the presence or absence of neuropilin-Fc to determine inhibition of VEGF-C/VEGFR-3 binding. The cells are then washed twice with cold phosphate buffered saline (PBS) containing 2 mM vanadate and 2 mM phenylmethylsulfonyl fluoride (PMSF), and lysed into PLCLB buffer (150 mM NaCl, 5% glycerol, 1% Triton X-100, 1.5 M MgCl2, and 50 mM Hepes, pH 7.5) containing 2 mM Vanadate, 2 mM PMSF, 0.07 U/ml Aprotinin, and 4 mg/ml leupeptin. The lysates are centrifuged for 10 min at 19 000 g, and incubated with the superantants for 2 h on ice with 2 μg/ml of monoclonal anti-VEGFR-3 antibodies (9D9f9) (Jussila et al., Cancer Res. 58:1599-1604. 1998), or alternatively with antibodies against the specific tag epitopes (1.1 mg/ml of anti-V5 antibodies (Invitrogen) or 5 μg/ml anti-Myc antibodies (BabCO). The immunocomplexes are incubated with protein A sepharose (Pharmacia) for 45 min with rotation at +4 °C and the sepharose beads washed three times with cold PLCLB buffer (2 mM vanadate, 2 mM PMSF). The bound polypeptides are separated by 7.5% SDS-PAGE and transferred to a Protran nitrocellulose filter (Schleicher & Schuell) using semi-dry transfer apparatus. After blocking with 5% BSA in TBS-T buffer (10 mM Tris pH 7.5, 150 mM NaCl, 0.1% Tween 20), the filters are stained with the phosphotyrosine-specific primary antibodies (Upstate Biotechnology), followed by biotinylated goat-anti-mouse immunoglobulins (Dako) and Biotin-Streptavidin HRP complex (Amersham) Phosphotyrosine-specific bands are visualized by enhanced chemiluminescence (ECL). To analyze the samples for the presence of VEGFR-3, the filters are stripped for 30 min at +55 °C in 100 mM 2-mercaptoethanol, 2% SDS, 62.5 mM Tris-HCl pH 6.7 with occasional agitation, and stained with 9D9f9 antibodies and HRP conjugated rabbit-anti-mouse immunoglobulins (Dako) for antigen detection. Reduced VEGFR-3 autophosphorylation is indicative of successful neuropilin-Fc-mediated inhibition of VEGF-C/VEGFR3 binding.

VEGF-C protein naturally secreted into media conditioned by a PC-3 prostatic adenocarcinoma cell line (ATCC CRL 1435) in serum-free Ham's F-12 Nutrient mixture (GIBCO) (containing 7% fetal calf serum (FCS)) (U.S. Patent 6,221,839) can be used to activate VEGFR3 expressing cells in vitro. For in vitro assay purposes, cells can be reseeded and grown in this medium, which is subsequently changed to serum-free medium. As shown in a previous experiment, pretreatment of the concentrated PC-3 conditioned medium with 50 microliters of VEGFR-3 extracellular domain coupled to CNBr-activated sepharose CL-4B (Pharmacia; about 1 mg of VEGFR-3EC domain/ml sepharose resin) completely abolished VEGFR-3 tyrosine phosphorylation (U.S. Patent 6,221,839). In a related experiment, the PC-3 conditioned media can be pre-treated with a neuropilin composition or control Fc coupled to sepharose. The cells can be lysed, immunoprecipitated using anti-VEGFR-3 antiserum, and analyzed by Western blot using anti-phosphotyrosine antibodies as previously described. The percent inhibition of VEGF-C binding and downstream VEGFR-3 autophosphorylation as a result of neuropilin sequestering of VEGF-C can be determined in this more biologically relevant situation.

The above experiments will also be carried out with relevant semaphorin proteins in conjunction with the neuropilin composition of the invention to determine the effects of another natural ligand for the neuropilin receptor on blocking VEGF-C/neuropilin receptor interactions. If the VEGF-C and semaphorin bind neuropilins in the same site on the receptor, there will be a subsequent increase in VEGF-C binding to VEGFR-3 and VEGFR-3 phosphorylation, due to the increase in VEGF-C unbound to the neuropilin-Fc. However, if the semaphorins and VEGF-C bind at different sites on the neuropilin receptor and do not inhibit each other's binding, then the amount of VEGF-C binding to VEGFR-3 will be comparable to binding in the absence of the semaphorins, i.e. with neuropilin-Fc alone. This assay will further define VEGF-C/neuropilin interactions.

The aforementioned in vitro cell-free and cell-based assays can also be performed with putative modulator compounds, eg cytokines that affect VEGF-C secretion (TNFa, TGFb, PDGF, TGFa, FGF-4, EGF, IL-1a IL-1b, IL-6) to determine the efficacy of the neuropilin composition at blocking VEGF-C activity in the presence of VEGF-C modulators which are biologically active in situations of

inflammation and tumor growth, comparing the neuropilin composition to current experimental cancer therapeutics.

EXAMPLE 4
EFFECTS OF NEUROPILIN-2/VEGF-C BINDING ON VEGF-C RELATED BIOLOGICAL FUNCTIONS

VEGF-C is intimately involved with many functions of lymphangiogenesis and endothelial cell growth. The influence of NRP-2 on such VEGF-C functions in vivo is investigated using the following assays:

A. Cell migration assay

For example, human microvascular endothelial cells (HMVEC) express VEGFR-3 and NRP-2, and such cells can be used to investigate the effect of soluble and membrane bound neuropilin receptors on such cells. Since neuropilins and VEGF/VEGFR interactions are thought to play a role in migration of cells, a cell migration assay using HMVEC or other suitable cells can be used to demonstrate stimulatory or inhibitory effects of neuropilin molecules.

Using a modified Boyden chamber assay, polycarbonate filter wells (Transwell, Costar, 8 micrometer pore) are coated with 50 micrograms/ml fibronectin (Sigma), 0.1% gelatin in PBS for 30 minutes at room temperature, followed by equilibration into DMEM/0.1% BSA at 37 degrees C for 1 hour. HMVEC (passage 4-9, 1 x 10^5 cells) naturally expressing VEGFR-3 and neuropilin receptors or endothelial cell lines recombinantly expressing VEGFR-3 and/or NRP-2 are plated in the upper chamber of the filter well and allowed to migrate to the undersides of the filters, toward the bottom chamber of the well, which contains serum-free media supplemented with prepro-VEGF-C, or enzymatically processed VEGF-C, in the presence of varying concentrations of neuropilin-1-Fc, neuropilin-2-Fc, and VEGFR-3-Fc protein. After 5 hours, cells adhering to the top of the transwell are removed with a cotton swab, and the cells that migrate to the underside of the filter are fixed and stained. For quantification of cell numbers, 6 randomly selected 400X microscope fields are counted per filter.

In another variation, the migration assay described above is carried out using porcine aortic endothelial cells (PAEC) stably transfected with constructs such as those described previously, to express NRP-2, VEGFR-3, or both NRP-2 and

VEGFR-3 (i.e. PAE/NRP-2, PAE/VEGFR-3, or PAE/NRP-2/VEGFR-3). PAEC are transfected using the method described in Soker et al. (Cell 92:735-745. 1998). Transfected PAEC (1.5 x 10^4 cells in serum free F12 media supplemented with 0.1% BSA) are plated in the upper wells of a Boyden chamber prepared with fibronectin as described above. Increasing concentrations of VEGF-C or VEGF-D are added to the wells of the lower chamber to induce migration of the endothelial cells. After 4hrs, the number of cells migrating through the filter is quantitated by phase microscopy.

An increase in migration and chemotaxis of NRP-2/VEGFR-3 double transfectants over NRP-2 or VEGFR-3 single transfectants indicates that the presence of neuropilin-2 enhances the ability of VEGF-C or VEGF-D to signal through VEGFR-3 and stimulate downstream biological effects, particluarly cell migration and, likely, angiogenesis or lymphangiogenesis.

Additionally, the porcine aortic endothelial cell migration assay is used to identify modulators of NRP-2/VEGFR-3/VEGF-C mediated stimulation of endothelial cells. Migration of PAE/NRP-2/VEGFR-3 expressing cells is assessed after the addition of compositions, such as soluble receptor peptides, proteins or other small molecules (e.g.monoclonal and bispecific antibodies or chemical compounds), to the lower wells of the Boyden chamber in combination with VEGF-C ligand. A decrease in migration as a result of the addition of any of the peptides, proteins or small molecules identifies that composition as an inhibitor of NRP-2/VEGFR-3 mediated chemotaxis.

B. Mitogen assay

Embyronic endothelial cells expressing VEGFR-3 alone, NRP-2 alone, or both VEGFR-3 and NRP-2 are cultured in the presence or absence of VEGF-C polypeptides, and potential modulators of this interactions such as semaphorins, more particularly Sema3F, as well as cytokines which may include but are not limited to TGF-β, TNF-α, IL-1α and IL-1β, IL-6, and PDGF, known to upregulate VEGF-C activity, to assay effects on cell growth using any cell growth or migration assay, such as assays that measure increase in cell number or assays that measure tritiated thymidine incorporation. See, e.g., Thompson et al., Am. J. Physiol. Heart Circ. Physiol., 281: H396-403 (2001).

EXAMPLE 5
ANGIOGENESIS ASSAYS

There continues to be a long-felt need for additional agents that can stimulate angiogenesis, e.g., to promote wound healing, or to promote successful tissue grafting and transplantation, as well as agents to inhibit angiogenesis (e.g., to inhibit growth of tumors). Moreover, various angiogenesis stimulators and inhibitors may work in concert through the same or different receptors, and on different portions of the circulatory system (e.g., arterieries or veins or capillaries; vascular or lymphatic). Angiogenesis assays are employed to measure the effects of neuropilin/VEGF-C interactions, on angiogenic processes, alone or in combination with other angiogenic and anti-angiogenic factors to determine preferred combination therapy involving neuropilins and other modulators. Exemplary procedures include the following.

A. *In vitro* assays for angiogenesis

1. Sprouting assay

HMVEC cells (passage 5-9) are grown to confluency on collagen coated beads (Pharmacia) for 5-7 days. The beads are plated in a gel matrix containing 5.5 mg/ml fibronectin (Sigma), 2 units/ml thrombin (Sigma), DMEM/2% fetal bovine serum (FBS) and the following test and control proteins: 20 ng/ml VEGF, 20 ng/ml VEGF-C, or growth factors plus 10 micrograms/ml neuropilin-2-Fc, and several combinations of angiogenic factors and Fc fusion proteins. Serum free media supplemented with test and control proteins is added to the gel matrix every 2 days and the number of endothelial cell sprouts exceeding bead length are counted and evaluated.

2. Migration assay

The transwell migration assay previously described may also be used in conjunction with the sprouting assay to determine the effects the neuropilin compositions of the invention have on the interactions of VEGF-C activators and cellular function. The effects of VEGF-Cs on cellular migration are assayed in response the neuropilin compositions of the invention, or in combination with known angiogenic or anti-angiogenic agents. A decrease in cellular migration due to the presence of the neuropilins after VEGF-C stimulation indicates that the invention provides a method for inhibiting angiogeneis.

This assay may also be carried out with cells that naturally express either VEGFR-3 or VEGFR-2, e.g. bovine endothelial cells which preferentially express VEGFR-2. Use of naturally occurring or transiently expressing cells displaying a specific receptor may determine that the neuropilin composition of the invention may be used to preferentially treat diseases involving aberrant activity of either VEGFR-3 or VEGFR-2.

B. *In vivo* assays for angiogenesis

1. Chorioallantoic Membrane (CAM) assay

Three-day old fertilized white Leghorn eggs are cracked, and chicken embryos with intact yolks are carefully placed in 20x100 mm plastic Petri dishes. After six days of incubation in 3% CO_2 at 37 degrees C, a disk of methylcellulose containing VEGF-C and various combinations of the neuropilin compositions, VEGFR-3, and neuropilin-2 and VEGFR-3 complexes, dried on a nylon mesh (3x3mm) is implanted on the CAM of individual embryos, to determine the influence of neuropilins on vascular development and potential uses thereof to promote or inhibit vascular formation. The nylon mesh disks are made by desiccation of 10 microliters of 0.45% methylcellulose (in H_2O). After 4-5 days of incubation, embryos and CAMs are examined for the formation of new blood vessels and lymphatic vessels in the field of the implanted disks by a stereoscope. Disks of methylcellulose containing PBS are used as negative controls. Antibodies that recognize both blood and lymphatic vessel cell surface molecules are used to further characterize the vessels.

2. Corneal assay

Corneal micropockets are created with a modified von Graefe cataract knife in both eyes of male 5- to 6-week-old C57BL6/J mice. A micropellet (0.35 x 0.35 mm) of sucrose aluminum sulfate (Bukh Meditec, Copenhagen, Denmark) coated with hydron polymer type NCC (IFN Science, New Brunswick, NJ) containing various concentrations of VEGF molecules (especially VEGF-C or VEGF-D) alone or in combination with: i) factors known to modulate vessel growth (e.g., 160 ng of VEGF, or 80 ng of FGF-2) ; ii) neuropilin polypeptides outlined above; or iii) neuropilin polypeptides in conjunction with natural neuropilin ligands such as semaphorins, e.g . Sema-3C and Sema3F, is implanted into each pocket. The pellet is positioned 0.6-0.8 mm from the limbus. After implantation, erythromycin /ophthamic ointment is applied to the eyes. Eyes are examined by a slit-lamp biomicroscope over

a course of 3-12 days. Vessel length and clock-hours of circumferential neovascularization and lymphangiogenesis are measured. Furthermore, eyes are cut into sections and are immunostained for blood vessel and/or lymphatic markers (LYVE-1 [Prevo et al., J. Biol. Chem., 276: 19420-19430 (2001)], podoplanin [Breiteneder-Geleff et al., Am. J. Pathol., 154: 385-94 (1999).] and VEGFR-3) to further characterize affected vessels.

EXAMPLE 6
IN VIVO TUMOR MODELS

There is mounting evidence that neuropilin receptors may play a significant role in tumor progression. Neuropilin-1 receptors are found in several tumor cell lines and trasfection of NRP-1 into AT2.1 cells can promote tumor growth and vascularization (Miao et al, FASEB J. 14: 2532-39. 2000). Additionally, investigation of neuropilin-2 expression in carcinoid tumors, slowly developing tumors derived from neuroendocrine cells in the digestive tract, illustrates that neuropilin-2 is actually expressed in normal tissue surrounding the tumor, but not in the center of the tumor itself (Cohen et al, Biochem. Biophys. Res. Comm. 284: 395-403. 2001), and it is established that neuroendocrine cells secrete VEGF-C, VEGF-D, and express VEGFR-3 on their cell surface (Partanen, et al., FASEB J 14:2087-96. 2000). Differential expression levels of these neuropilins in association with VEGF molecules, which are often correlative with vascular density and tumor progression, in and around tumors could be indicative of tumor progression or regression.

A. Ectopic Tumor Implantation

Six- to 8-week-old nude (nu/nu) mice (SLC, Shizuoka, Japan) undergo subcutaneous transplantation of C6 rat glioblastoma cells or PC-3 prostate cancer cells in 0.1 mL phosphate-buffered saline (PBS) on the right flank. The neuropilin polypeptides outlined previously are administered to the animals at various concentrations and dosing regimens. Tumor size is measured in 2 dimensions, and tumor volume is calculated using the formula, width2 x length/2. After 14 days, the mice are humanely killed and autopsied to evaluate the quantity and physiology of tumor vasculature in response to VEGF-C inhibition by neuropilin polypeptides.

It will be apparent that the assay can also be performed using other tumor cell lines implanted in nude mice or other mouse strains. Use of wild type mice

implanted with LLC lung cancer cells and B16 melanoma cells is specifically contemplated.

B Orthotopic tumor implantation

Approximately 1 x 10^7 MCF-7 breast cancer cells in PBS are inoculated into the fat pads of the second (axillar) mammary gland of ovarectomized SCID mice or nude mice, carrying s.c. 60-day slow-release pellets containing 0.72 mg of 17ß-estradiol (Innovative Research of America). The ovarectomy and implantation of the pellets are done 4-8 days before tumor cell inoculation. The neuropilin polypeptides and VEGF-C polypeptides outlined previously, as well as semaphorins, specifically Sema3C and Sema3F, are administered to the animals at various concentrations and dosing regimens. Tumor size is measured in 2 dimensions, and tumor volume is calculated using the formula, width 2 x length/2. After 14 days, the mice are humanely killed and autopsied to evaluate the quantity and physiology of tumor vasculature.

A similar protocol is employed wherein PC-3 cells are implanted into the prostate of male mice.

C. Lymphatic metastasis model

VEGF-C/VEGFR3 interactions are often associated in adult tissue with the organization and growth of lymphatic vessels, thus the presence of neuropilin receptor at these sites may be involved in the metastic nature of some cancers. The following protocol indicates the ability of neuropilin polypeptides, especially neuropilin-2 polypeptides, or fragments thereof for inhibition of lymphatic metastasis.

MDA-MB-435 breast cancer cells are injected bilaterally into the second mammary fat pads of athymic, female, eight week old nude mice. The cells often metastasize to lymph node by 12 weeks. Initially, the role of neuropilin-2 binding to VEGF-C and VEGFR-3 in tumor metastasis can be assessed using modulators of neuropilin-VEGF-C binding determined previously, especially contemplated are the semaphorins. A decrease in metastasis correlating with NRP-2 blockade indicates NRP-2 is critical in tumor metastasis. The modulators of neuropilin-VEGF-C binding determined previously [by the invention] are then administered to the animals at various concentrations and dosing regimens. Moreover, the neuropilin-2 polypeptides are administered in combination with other

materials for reducing tumor metastasis. See, e.g., International Patent Publication No. WO 00/21560, incorporated herein by reference in its entirety. Mice are sacrificed after 12 weeks and lymph nodes are investigated by histologic analysis. Decrease in lymphatic vessels and tumor spread as a result of administration of the neuropilin compositions indicate the invention may be a therapeutic compound in the prevention of tumor metastasis.

EXAMPLE 7
ASSESSMENT OF VEGF-C ON GROWTH CONE COLLAPSE BY COLLAGEN REPULSION ASSAY

The constitutive expression of semaphorins in the central nervous system has been proposed as a primary factor in the lack of regeneration of nerves in this area. Regeneration of peripheral nerves after nerve insult, such as sciatic nerve crush, is made possible by the downregulation of semaphorin-3A expression immediately following injury. Sema3A expression returns to baseline levels after approximately 36 days following injury, but this extended period of decreased semaphorin expression allows for the growth and regeneration of the peripheral nerve into the area of damage before the regrowth is halted by semaphorin activity (reviewed in Pasterkamp and Verhaagen, Brain Res. Rev. 35: 36-54. 2000). While numerous semaphorins are extensively expressed in the CNS and PNS, semaphorin-3F, the primary ligand for neuropilin-2, demonstrates wide distribution in human brain, and has even been found to be overexpressed in certain areas of the brain in Alzheimer's patients (Hirsch et al, Brain Res. 823:67-79. 1999). The newly discovered interaction of VEGF-C binding to NRP-2 may provide a factor for specifically inhibiting the actions of sema-3F activty in halting neural regeneration in many neurodegenerative diseases such as Alzheimer's or macular degeneration.

Superior cervical ganglia (SCG) are dissected out of E13.5 or E15.5-17.5 rat or mouse embryos according to the method of Chen et al (Neuron, 25:43-56. 2000) and Giger et al (Neuron, 25:29-41. 2000) for use in a collagen repulsion assay. Following dissection, hindbrain-midbrain junction explants are co-cultured with COS cells recombinantly modified to express Alkaline phosphatase conjugated Sema3F or mock transfected COS cells in collagen matrices in culture medium [OPTI-MEM and F12 at 70:25, supplemented with 1% P/S, Glutamax (Gibco), 5% FCS and 40mM

glucose] for 48h. Neurite extension is quantitated using the protocol outlined by Giger et al (Neuron, 25:29-41. 2000), briefly described by determining the percentage of neurite extension beyond a defined point in the culture matrix. Neurite extension can be measured in the presence of varying concentrations of a VEGF-C composition as compared to in the absence of a VEGF-C composition and the subsequent increase of neurite extension as a result of VEGF-C addition to the culture and blockade of Sema3F interaction with neuropilin-2 can be assessed.

The effects of Sema3F inhibition as a result of the present invention may be extrapolated into treatments for several diseases wherein neuronal regeneration is prohibited by the presence of semaphorins, for example scarring after cranial nerve damage, and perhaps in the brains of Alzheimer's patients.

Variations to the examples given above will be apparent and are considered aspects of the invention within the claims.

For example, the materials and methods described in the preceding Examples are useful and readily adapted for screening for new modulators of the polypeptide interactions described herein, and for demonstrating the effects of such new modulators in cell-based systems and in vivo. In other words, the procedures in the materials and methods of the Examples are useful for identifying modulators and screening the modulators for activity in vitro and in vivo.

By way of illustration, Example 1 describes an experimental protocol wherein VEGF-C binding to neuropilins was investigated. Similar binding experiments can be performed in which a test agent is added to the binding experiment at one or more test agent concentrations, to determine if the test agent modulates (increases or decreases) the measurable binding between VEGF-C and the neuropilin. Example 2 describes an experimental protocol wherein VEGFR-3 binding to neuropilins was investigated. Similar binding experiments can be perfomed in which a test agent is included in the reaction to determine if the test agent modulates (increases or decreases) the measurable binding between VEGFR-3 and the neuropilin. Test agents that are identified as modulators in initial binding assays can be included in cell-based and in vivo assays that are provided in subsequent Examples, to measure the biological effects of the test agents on cells that express

receptors of interest (e.g., VEGFR-3 or neuropilin-expressing cells) or on biological systems and organisms.

Similarly, a number of the Examples describe using a soluble form of neuropilin receptor or other protein in experiments that further prove binding relationships between molecules described herein for the first time. These experiments also demonstrate that molecules that bind one or both members of a ligand/receptor pair or receptor/co-receptor pair can be added to a system to modulate (especially inhibit) the ability of the binding pair to interact. For example, soluble NRP molecules are used in Example 3 to modulate (inhibit) VEGF-C or VEGF-D binding to VEGFR-3 or VEGFR-2. The disruption of VEGF-C or VEGF-D binding to their respective VEGFR receptors has practical applications for treatment of numerous diseases characterized by undesirable ligand-mediated stimulation of VEGFR-3 or VEGFR-2. Similar binding experiments can be performed in which a test agent suspected of modulating the same binding reactions is substituted for the soluble NRP molecule. In this way, the materials and methods of the Examples are used to identify and veryify the therapeutic value of test agents.

Practicing the Examples using small organic or inorganic molecules, peptide libraries, and chemical compound libraries in place of the neuropilin or VEGF-C polypeptides is particularly contemplated. Small molecules and chemical compounds identified by the invention as modulators of neuropilin-VEGF-C and/or neuropilin/VEGFR-3 interactions will be useful as therapeutic compositions to treat situations of aberrant neuropilin-VEGF-C interactions, and in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells mediated by VEGF-C binding to NRP-2/ VEGFR-3 complexes.

The foregoing describes and exemplifies the invention but is not intended to limit the invention defined by the claims which follow.

CLAIMS

What is claimed is:

1. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGF-C polypeptide comprising steps of:

a) contacting a neuropilin composition that comprises a neuropilin polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

2. A method according to claim 1, further comprising a step of:

(d) making a modulator composition by formulating a modulator identified according to step (c) in a pharmaceutically acceptable carrier.

3. A method according to claim 2, further comprising a step of:

(e) administering the modulator composition to an animal that comprises cells that express the neuropilin receptor, and determining physiological effects of the modulator composition in the animal.

4. A method according to any one of claims 1-3 wherein the neuropilin receptor composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a neuropilin receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing neuropilin polypeptides; and

(c) a cell recombinantly modified to express increased levels of neuropilin receptor polypeptide on the cell surface.

5. A method according to any one of claims 1-3, wherein the neuropilin receptor composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment bound to a solid support.

6. A method according to claim 1, wherein the neuropilin receptor composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment fused to an immunoglobulin Fc fragment.

7. A method according to any one of claims 1-6, wherein the neuropilin composition comprises a mammalian neuropilin-2 polypeptide .

8. A method according to claim 7, wherein the neuropilin-2 polypeptide is human.

9. A method according to any one of claims 1-6, wherein the neuropilin composition comprises a mammalian neuropilin-1 polypeptide.

10. A method according to claim 1 wherein the VEGF-C composition comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment of the prepro-VEGF-C polypeptide, that binds the neuropilin receptor.

11. A method according to claim 10, wherein the prepro-VEGF-C polypeptide is human.

12. A method according to claim 10, wherein the VEGF-C composition comprises a fragment of human prepro-VEGFC that contains amino acids 103-227 of SEQ ID NO: 24.

13. A method according to any one of claims 10-12, wherein the VEGF-C composition comprises amino acids 32 to 227 of the human prepro-VEGF-C sequence of SEQ. ID. NO: 24.

14. A method according to claim 1, wherein the VEGF-C composition comprises a conditioned media from a cell recombinantly modified to express and secrete a VEGF-C polypeptide.

15. A method according to any one of claims 1-3, wherein the neuropilin composition comprises a cell recombinantly modified to express increased amounts of a neuropilin receptor on its surface, and wherein the detecting step comprises measuring a VEGF-C binding-induced physiological change in the cell.

16. A method for screening for selectivity of a modulator of VEGF-C biological activity, comprising steps of:

a) contacting a VEGF-C composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the neuropilin;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGFR-3 extracellular domain; and

(ii) a polypeptide comprising a VEGFR-2 extracellular domain; and

(c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

17. A method for screening for selectivity of a modulator of neuropilin biological activity, comprising steps of:

a) contacting a neuropilin composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the VEGF-C;

b) contacting a neuropilin composition with a composition comprising a neuropilin binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the binding partner; and wherein the binding partner is a polypeptide comprising an amino acid sequence selected from the group consisting of:

an amino acid sequence of a semaphorin 3 polypeptide; a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and an amino acid sequence of a plexin polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

18. A method according to claim 17 wherein the binding partner is a human semaphorin.

19. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

20. A method according to claim 19 wherein the VEGFR-3 composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a VEGFR-3 receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing VEGFR-3 polypeptides; and

(c) a cell recombinantly modified to express increased levels of VEGFR-3 receptor on the cell surface.

21. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment bound to a solid support.

22. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment fused to an immunoglobulin Fc fragment.

23. A method according to any one of claims 19-22, wherein the VEGFR-3 is a mammalian VEGFR-3.

24. A method according to claim 23, wherein the VEGFR-3 is human.

25. A method for screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of the compound and detecting binding between the VEGFR-3 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and

(ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

26. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a neuropilin polypeptide or fragment thereof that binds to the VEGF-C polypeptide;

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin in the mammalian organism.

27. A method according to claim 26, wherein the mammalian organism is human.

28. A method according to claim 23, further comprising administering a second agent to the patient for modulating endothelial growth, migration, or proliferation through a neuropilin receptor, said second agent comprising a polypeptide comprising an amino acid sequence selected from the group consisting of: a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a VEGF-E amino acid sequence, a PlGF amino acid sequence, a semaphorin 3A amino acid sequence, semaphorin 3C amino acid sequence, and a semaphorin 3F amino acid sequence.

29. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor in the mammalian organism.

30. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGF-C polypeptide.

31. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor and a VEGFR-3 polypeptide; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and a VEGFR-3 polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor and the VEGFR-3 polypeptide in the mammalian organism.

32. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGFR-3 polypeptide.

33. A method of modulating neuronal growth, or neuronal scarring in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin receptor.

34. A method according to claim 33, wherein the mammalian organism is human.

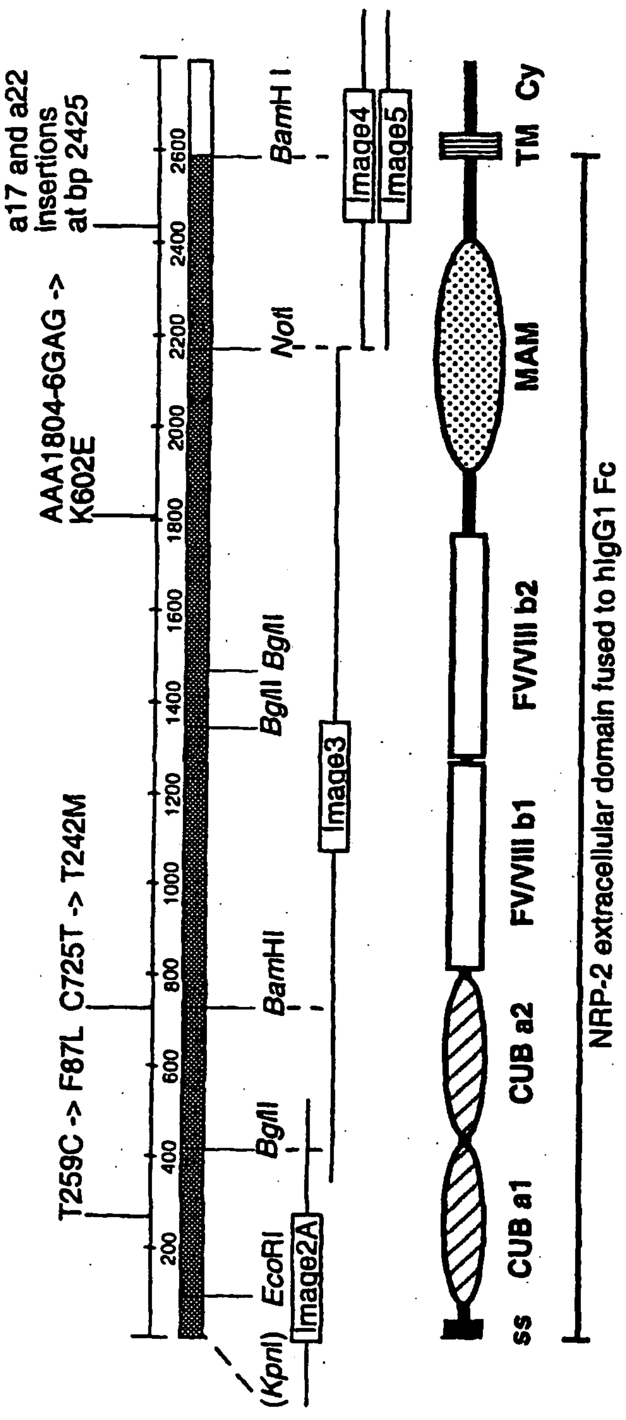
35. A method according to claim 33, wherein the cells comprise neuronal cells that express neuropilin-2.

36. A method according to any one of claims 33, wherein the organism has a disease characterized by aberrant growth of neuronal cells involved in scarring and neural degeneration.

37. A method according to claim 36, wherein the disease comprises a neurodegenerative disorder, more specifically Alzheimer's disease.

38. A polypeptide comprising a fragment of a VEGF-C that binds to a neuropilin receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor.

Figure 1.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915 920

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Ala Pro Ala Gly Ala Phe Arg Asn Asp Glu Cys Gly Asp Thr Ile Lys
20 25 30

Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr
35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr
50 55 60

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn
85 90 95

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Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val
            100                 105                 110

Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu
        115                 120                 125

Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly
    130                 135                 140

Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser
145                 150                 155                 160

Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile
                165                 170                 175

Val Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe
            180                 185                 190

Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr
        195                 200                 205

Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile
    210                 215                 220

Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser
225                 230                 235                 240

Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu
                245                 250                 255

Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp
            260                 265                 270

Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser
        275                 280                 285

Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu
    290                 295                 300

Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp
305                 310                 315                 320

Ser Tyr Arg Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val
                325                 330                 335

Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys
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340 345 350

Tyr Tyr Val Lys Thr Tyr Lys Ile Asp Val Ser Ser Asn Gly Glu Asp
355 360 365

Trp Ile Thr Ile Lys Glu Gly Asn Lys Pro Val Leu Phe Gln Gly Asn
370 375 380

Thr Asn Pro Thr Asp Val Val Val Ala Val Phe Pro Lys Pro Leu Ile
385 390 395 400

Thr Arg Phe Val Arg Ile Lys Pro Ala Thr Trp Glu Thr Gly Ile Ser
405 410 415

Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser
420 425 430

Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr
435 440 445

Ser Ser Asn Gln Gly Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu
450 455 460

Val Thr Ser Arg Ser Gly Trp Ala Leu Pro Pro Ala Pro His Ser Tyr
465 470 475 480

Ile Asn Glu Trp Leu Gln Ile Asp Leu Gly Glu Glu Lys Ile Val Arg
485 490 495

Gly Ile Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met
500 505 510

Arg Lys Phe Lys Ile Gly Tyr Ser Asn Asn Gly Ser Asp Trp Lys Met
515 520 525

Ile Met Asp Asp Ser Lys Arg Lys Ala Lys Ser Phe Glu Gly Asn Asn
530 535 540

Asn Tyr Asp Thr Pro Glu Leu Arg Thr Phe Pro Ala Leu Ser Thr Arg
545 550 555 560

Phe Ile Arg Ile Tyr Pro Glu Arg Ala Thr His Gly Gly Leu Gly Leu
565 570 575

Arg Met Glu Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro
580 585 590

Thr Thr Pro Asn Gly Asn Leu Val Asp Glu Cys Asp Asp Asp Gln Ala
595 600 605

Asn Cys His Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr
610 615 620

Thr Val Leu Ala Thr Glu Lys Pro Thr Val Ile Asp Ser Thr Ile Gln
625 630 635 640

Ser Glu Phe Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser
645 650 655

His Lys Thr Phe Cys His Trp Glu His Asp Asn His Val Gln Leu Lys
660 665 670

Trp Ser Val Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly
675 680 685

Asp Gly Asn Phe Ile Tyr Ser Gln Ala Asp Glu Asn Gln Lys Gly Lys
690 695 700

Val Ala Arg Leu Val Ser Pro Val Val Tyr Ser Gln Asn Ser Ala His
705 710 715 720

Cys Met Thr Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu
725 730 735

Arg Val Lys Leu Arg Tyr Gln Lys Pro Glu Glu Tyr Asp Gln Leu Val
740 745 750

Trp Met Ala Ile Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val
755 760 765

Leu Leu His Lys Ser Leu Lys Leu Tyr Gln Val Ile Phe Glu Gly Glu
770 775 780

Ile Gly Lys Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile
785 790 795 800

Asn Asn His Ile Ser Gln Glu Asp Cys Ala Lys Pro Ala Asp Leu Asp
805 810 815

Lys Lys Asn Pro Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly
820 825 830

Tyr Glu Gly Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly
835 840 845

Asn Val Leu Lys Thr Leu Glu Pro Ile Leu Ile Thr Ile Ile Ala Met
850 855 860

Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr
865 870 875 880

Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu
885 890 895

Glu Asn Tyr Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp
900 905 910

Lys Leu Asn Thr Gln Ser Thr Tyr Ser Glu Ala
915 920

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aga cac caa gtg aga ggc caa cca gac cca ccg tgc gga ggt cgt ttg 96
Arg His Gln Val Arg Gly Gln Pro Asp Pro Pro Cys Gly Gly Arg Leu
20 25 30

aat tcc aaa gat gct ggc tat atc acc tct ccc ggt tac ccc cag gac 144
Asn Ser Lys Asp Ala Gly Tyr Ile Thr Ser Pro Gly Tyr Pro Gln Asp
35 40 45

tac ccc tcc cac cag aac tgc gag tgg att gtt tac gcc ccc gaa ccc 192
Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro
50 55 60

aac cag aag att gtc ctc aac ttc aac cct cac ttt gaa atc gag aag 240
Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys
65 70 75 80

cac gac tgc aag tat gac ttt atc gag att cgg gat ggg gac agt gaa 288

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His Asp Cys Lys Tyr Asp Phe Ile Glu Ile Arg Asp Gly Asp Ser Glu
                85                  90                  95

tcc gca gac ctc ctg ggc aaa cac tgt ggg aac atc gcc ccg ccc acc      336
Ser Ala Asp Leu Leu Gly Lys His Cys Gly Asn Ile Ala Pro Pro Thr
            100                 105                 110

atc atc tcc tcg ggc tcc atg ctc tac atc aag ttc acc tcc gac tac      384
Ile Ile Ser Ser Gly Ser Met Leu Tyr Ile Lys Phe Thr Ser Asp Tyr
        115                 120                 125

gcc cgg cag ggg gca ggc ttc tct ctg cgc tac gag atc ttc aag aca      432
Ala Arg Gln Gly Ala Gly Phe Ser Leu Arg Tyr Glu Ile Phe Lys Thr
    130                 135                 140

ggc tct gaa gat tgc tca aaa aac ttc aca agc ccc aac ggg acc atc      480
Gly Ser Glu Asp Cys Ser Lys Asn Phe Thr Ser Pro Asn Gly Thr Ile
145                 150                 155                 160

gaa tct cct ggg ttt cct gag aag tat cca cac aac ttg gac tgc acc      528
Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr
                165                 170                 175

ttt acc atc ctg gcc aaa ccc aag atg gag atc atc ctg cag ttc ctg      576
Phe Thr Ile Leu Ala Lys Pro Lys Met Glu Ile Ile Leu Gln Phe Leu
            180                 185                 190

atc ttt gac ctg gag cat gac cct ttg cag gtg gga gag ggg gac tgc      624
Ile Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys
        195                 200                 205

aag tac gat tgg ctg gac atc tgg gat ggc att cca cat gtt ggc ccc      672
Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro
    210                 215                 220

ctg att ggc aag tac tgt ggg acc aaa aca ccc tct gaa ctt cgt tca      720
Leu Ile Gly Lys Tyr Cys Gly Thr Lys Thr Pro Ser Glu Leu Arg Ser
225                 230                 235                 240

tcg acg ggg atc ctc tcc ctg acc ttt cac acg gac atg gcg gtg gcc      768
Ser Thr Gly Ile Leu Ser Leu Thr Phe His Thr Asp Met Ala Val Ala
                245                 250                 255

aag gat ggc ttc tct gcg cgt tac tac ctg gtc cac caa gag cca cta      816
Lys Asp Gly Phe Ser Ala Arg Tyr Tyr Leu Val His Gln Glu Pro Leu
            260                 265                 270

gag aac ttt cag tgc aat gtt cct ctg ggc atg gag tct ggc cgg att      864
Glu Asn Phe Gln Cys Asn Val Pro Leu Gly Met Glu Ser Gly Arg Ile
        275                 280                 285

gct aat gaa cag atc agt gcc tca tct acc tac tct gat ggg agg tgg      912
Ala Asn Glu Gln Ile Ser Ala Ser Ser Thr Tyr Ser Asp Gly Arg Trp
    290                 295                 300

acc cct caa caa agc cgg ctc cat ggt gat gac aat ggc tgg acc ccc      960
Thr Pro Gln Gln Ser Arg Leu His Gly Asp Asp Asn Gly Trp Thr Pro
305                 310                 315                 320

aac ttg gat tcc aac aag gag tat ctc cag gtg gac ctg cgc ttt tta     1008
Asn Leu Asp Ser Asn Lys Glu Tyr Leu Gln Val Asp Leu Arg Phe Leu
                325                 330                 335
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acc atg ctc acg gcc atc gca aca cag gga gcg att tcc agg gaa aca      1056
Thr Met Leu Thr Ala Ile Ala Thr Gln Gly Ala Ile Ser Arg Glu Thr
            340                 345                 350

cag aat ggc tac tac gtc aaa tcc tac aag ctg gaa gtc agc act aat      1104
Gln Asn Gly Tyr Tyr Val Lys Ser Tyr Lys Leu Glu Val Ser Thr Asn
        355                 360                 365

gga gag gac tgg atg gtg tac cgg cat ggc aaa aac cac aag gta ttt      1152
Gly Glu Asp Trp Met Val Tyr Arg His Gly Lys Asn His Lys Val Phe
    370                 375                 380

caa gcc aac aac gat gca act gag gtg gtt ctg aac aag ctc cac gct      1200
Gln Ala Asn Asn Asp Ala Thr Glu Val Val Leu Asn Lys Leu His Ala
385                 390                 395                 400

cca ctg ctg aca agg ttt gtt aga atc cgc cct cag acc tgg cac tca      1248
Pro Leu Leu Thr Arg Phe Val Arg Ile Arg Pro Gln Thr Trp His Ser
                405                 410                 415

ggt atc gcc ctc cgg ctg gag ctc ttc ggc tgc cgg gtc aca gat gct      1296
Gly Ile Ala Leu Arg Leu Glu Leu Phe Gly Cys Arg Val Thr Asp Ala
            420                 425                 430

ccc tgc tcc aac atg ctg ggg atg ctc tca ggc ctc att gca gac tcc      1344
Pro Cys Ser Asn Met Leu Gly Met Leu Ser Gly Leu Ile Ala Asp Ser
        435                 440                 445


cag atc tcc gcc tct tcc acc cag gaa tac ctc tgg agc ccc agt gca      1392
Gln Ile Ser Ala Ser Ser Thr Gln Glu Tyr Leu Trp Ser Pro Ser Ala
    450                 455                 460

gcc cgc ctg gtc agc agc cgc tcg ggc tgg ttc cct cga atc cct cag      1440
Ala Arg Leu Val Ser Ser Arg Ser Gly Trp Phe Pro Arg Ile Pro Gln
465                 470                 475                 480

gcc cag ccc ggt gag gag tgg ctt cag gta gat ctg gga aca ccc aag      1488
Ala Gln Pro Gly Glu Glu Trp Leu Gln Val Asp Leu Gly Thr Pro Lys
                485                 490                 495

aca gtg aaa ggt gtc atc atc cag gga gcc cgc gga gga gac agt atc      1536
Thr Val Lys Gly Val Ile Ile Gln Gly Ala Arg Gly Gly Asp Ser Ile
            500                 505                 510

act gct gtg gaa gcc aga gca ttt gtg cgc aag ttc aaa gtc tcc tac      1584
Thr Ala Val Glu Ala Arg Ala Phe Val Arg Lys Phe Lys Val Ser Tyr
        515                 520                 525

agc cta aac ggc aag gac tgg gaa tac att cag gac ccc agg acc cag      1632
Ser Leu Asn Gly Lys Asp Trp Glu Tyr Ile Gln Asp Pro Arg Thr Gln
    530                 535                 540

cag cca aag ctg ttc gaa ggg aac atg cac tat gac acc cct gac atc      1680
Gln Pro Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile
545                 550                 555                 560

cga agg ttt gac ccc att ccg gca cag tat gtg cgg gta tac ccg gag      1728
Arg Arg Phe Asp Pro Ile Pro Ala Gln Tyr Val Arg Val Tyr Pro Glu
                565                 570                 575

agg tgg tcg ccg gcg ggg att ggg atg cgg ctg gag gtg ctg ggc tgt      1776
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Arg Trp Ser Pro Ala Gly Ile Gly Met Arg Leu Glu Val Leu Gly Cys
            580                 585                 590

gac tgg aca gac tcc aag ccc acg gta aaa acg ctg gga ccc act gtg      1824
Asp Trp Thr Asp Ser Lys Pro Thr Val Lys Thr Leu Gly Pro Thr Val
        595                 600                 605

aag agc gaa gag aca acc acc ccc tac ccc acc gaa gag gag gcc aca      1872
Lys Ser Glu Glu Thr Thr Thr Pro Tyr Pro Thr Glu Glu Glu Ala Thr
    610                 615                 620

gag tgt ggg gag aac tgc agc ttt gag gat gac aaa gat ttg cag ctc      1920
Glu Cys Gly Glu Asn Cys Ser Phe Glu Asp Asp Lys Asp Leu Gln Leu
625                 630                 635                 640

cct tcg gga ttc aat tgc aac ttc gat ttc ctc gag gag ccc tgt ggt      1968
Pro Ser Gly Phe Asn Cys Asn Phe Asp Phe Leu Glu Glu Pro Cys Gly
                645                 650                 655

tgg atg tat gac cat gcc aag tgg ctc cgg acc acc tgg gcc agc agc      2016
Trp Met Tyr Asp His Ala Lys Trp Leu Arg Thr Thr Trp Ala Ser Ser
            660                 665                 670

tcc agc cca aac gac cgg acg ttt cca gat gac agg aat ttc ttg cgg      2064
Ser Ser Pro Asn Asp Arg Thr Phe Pro Asp Asp Arg Asn Phe Leu Arg
        675                 680                 685

ctg cag agt gac agc cag aga gag ggc cag tat gcc cgg ctc atc agc      2112
Leu Gln Ser Asp Ser Gln Arg Glu Gly Gln Tyr Ala Arg Leu Ile Ser
    690                 695                 700


ccc cct gtc cac ctg ccc cga agc ccg gtg tgc atg gag ttc cag tac      2160
Pro Pro Val His Leu Pro Arg Ser Pro Val Cys Met Glu Phe Gln Tyr
705                 710                 715                 720

cag gcc acg ggc ggc cgc ggg gtg gcg ctg cag gtg gtg cgg gaa gcc      2208
Gln Ala Thr Gly Gly Arg Gly Val Ala Leu Gln Val Val Arg Glu Ala
                725                 730                 735

agc cag gag agc aag ttg ctg tgg gtc atc cgt gag gac cag ggc ggc      2256
Ser Gln Glu Ser Lys Leu Leu Trp Val Ile Arg Glu Asp Gln Gly Gly
            740                 745                 750

gag tgg aag cac ggg cgg atc atc ctg ccc agc tac gac atg gag tac      2304
Glu Trp Lys His Gly Arg Ile Ile Leu Pro Ser Tyr Asp Met Glu Tyr
        755                 760                 765

cag att gtg ttc gag gga gtg ata ggg aaa gga cgt tcc gga gag att      2352
Gln Ile Val Phe Glu Gly Val Ile Gly Lys Gly Arg Ser Gly Glu Ile
    770                 775                 780

gcc att gat gac att cgg ata agc act gat gtc cca ctg gag aac tgc      2400
Ala Ile Asp Asp Ile Arg Ile Ser Thr Asp Val Pro Leu Glu Asn Cys
785                 790                 795                 800

atg gaa ccc atc tcg gct ttt gca gtg gac atc cca gaa ata cat gag      2448
Met Glu Pro Ile Ser Ala Phe Ala Val Asp Ile Pro Glu Ile His Glu
                805                 810                 815

aga gaa gga tat gaa gat gaa att gat gat gaa tac gag gtg gac tgg      2496
Arg Glu Gly Tyr Glu Asp Glu Ile Asp Asp Glu Tyr Glu Val Asp Trp
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            820                     825                     830

agc aat tct tct tct gca acc tca ggg tct ggc gcc ccc tcg acc gac      2544
Ser Asn Ser Ser Ser Ala Thr Ser Gly Ser Gly Ala Pro Ser Thr Asp
        835                     840                     845

aaa gaa aag agc tgg ctg tac acc ctg gat ccc atc ctc atc acc atc      2592
Lys Glu Lys Ser Trp Leu Tyr Thr Leu Asp Pro Ile Leu Ile Thr Ile
    850                     855                     860

atc gcc atg agc tca ctg ggc gtc ctc ctg ggg gcc acc tgt gca ggc      2640
Ile Ala Met Ser Ser Leu Gly Val Leu Leu Gly Ala Thr Cys Ala Gly
865                     870                     875                     880

ctc ctg ctc tac tgc acc tgt tcc tac tcg ggc ctg agc tcc cga agc      2688
Leu Leu Leu Tyr Cys Thr Cys Ser Tyr Ser Gly Leu Ser Ser Arg Ser
                885                     890                     895

tgc acc aca ctg gag aac tac aac ttc gag ctc tac gat ggc ctt aag      2736
Cys Thr Thr Leu Glu Asn Tyr Asn Phe Glu Leu Tyr Asp Gly Leu Lys
            900                     905                     910

cac aag gtc aag atg aac cac caa aag tgc tgc tcc gag gca tga          2781
His Lys Val Lys Met Asn His Gln Lys Cys Cys Ser Glu Ala
        915                     920                     925
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<212> PRT

<213> Homo sapiens

<400> 4

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Arg His Gln Val Arg Gly Gln Pro Asp Pro Pro Cys Gly Gly Arg Leu
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Asn Ser Lys Asp Ala Gly Tyr Ile Thr Ser Pro Gly Tyr Pro Gln Asp
        35                  40                  45

Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro
    50                  55                  60

Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys
65                  70                  75                  80

His Asp Cys Lys Tyr Asp Phe Ile Glu Ile Arg Asp Gly Asp Ser Glu
                85                  90                  95
```

Ser Ala Asp Leu Leu Gly Lys His Cys Gly Asn Ile Ala Pro Pro Thr
100 105 110

Ile Ile Ser Ser Gly Ser Met Leu Tyr Ile Lys Phe Thr Ser Asp Tyr
115 120 125

Ala Arg Gln Gly Ala Gly Phe Ser Leu Arg Tyr Glu Ile Phe Lys Thr
130 135 140

Gly Ser Glu Asp Cys Ser Lys Asn Phe Thr Ser Pro Asn Gly Thr Ile
145 150 155 160

Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr
165 170 175

Phe Thr Ile Leu Ala Lys Pro Lys Met Glu Ile Ile Leu Gln Phe Leu
180 185 190

Ile Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys
195 200 205

Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro
210 215 220

Leu Ile Gly Lys Tyr Cys Gly Thr Lys Thr Pro Ser Glu Leu Arg Ser
225 230 235 240

Ser Thr Gly Ile Leu Ser Leu Thr Phe His Thr Asp Met Ala Val Ala
245 250 255

Lys Asp Gly Phe Ser Ala Arg Tyr Tyr Leu Val His Gln Glu Pro Leu
260 265 270

Glu Asn Phe Gln Cys Asn Val Pro Leu Gly Met Glu Ser Gly Arg Ile
275 280 285

Ala Asn Glu Gln Ile Ser Ala Ser Ser Thr Tyr Ser Asp Gly Arg Trp
290 295 300

Thr Pro Gln Gln Ser Arg Leu His Gly Asp Asp Asn Gly Trp Thr Pro
305 310 315 320

Asn Leu Asp Ser Asn Lys Glu Tyr Leu Gln Val Asp Leu Arg Phe Leu
325 330 335

Thr Met Leu Thr Ala Ile Ala Thr Gln Gly Ala Ile Ser Arg Glu Thr
340 345 350

Gln Asn Gly Tyr Tyr Val Lys Ser Tyr Lys Leu Glu Val Ser Thr Asn
355 360 365

Gly Glu Asp Trp Met Val Tyr Arg His Gly Lys Asn His Lys Val Phe
370 375 380

Gln Ala Asn Asn Asp Ala Thr Glu Val Val Leu Asn Lys Leu His Ala
385 390 395 400

Pro Leu Leu Thr Arg Phe Val Arg Ile Arg Pro Gln Thr Trp His Ser
405 410 415

Gly Ile Ala Leu Arg Leu Glu Leu Phe Gly Cys Arg Val Thr Asp Ala
420 425 430

Pro Cys Ser Asn Met Leu Gly Met Leu Ser Gly Leu Ile Ala Asp Ser
435 440 445

Gln Ile Ser Ala Ser Ser Thr Gln Glu Tyr Leu Trp Ser Pro Ser Ala
450 455 460

Ala Arg Leu Val Ser Ser Arg Ser Gly Trp Phe Pro Arg Ile Pro Gln
465 470 475 480

Ala Gln Pro Gly Glu Glu Trp Leu Gln Val Asp Leu Gly Thr Pro Lys
485 490 495

Thr Val Lys Gly Val Ile Ile Gln Gly Ala Arg Gly Gly Asp Ser Ile
500 505 510

Thr Ala Val Glu Ala Arg Ala Phe Val Arg Lys Phe Lys Val Ser Tyr
515 520 525

Ser Leu Asn Gly Lys Asp Trp Glu Tyr Ile Gln Asp Pro Arg Thr Gln
530 535 540

Gln Pro Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile
545 550 555 560

Arg Arg Phe Asp Pro Ile Pro Ala Gln Tyr Val Arg Val Tyr Pro Glu
565 570 575

Arg Trp Ser Pro Ala Gly Ile Gly Met Arg Leu Glu Val Leu Gly Cys
580 585 590

Asp Trp Thr Asp Ser Lys Pro Thr Val Lys Thr Leu Gly Pro Thr Val
595 600 605

Lys Ser Glu Glu Thr Thr Thr Pro Tyr Pro Thr Glu Glu Glu Ala Thr
610 615 620

Glu Cys Gly Glu Asn Cys Ser Phe Glu Asp Asp Lys Asp Leu Gln Leu
625 630 635 640

Pro Ser Gly Phe Asn Cys Asn Phe Asp Phe Leu Glu Glu Pro Cys Gly
645 650 655

Trp Met Tyr Asp His Ala Lys Trp Leu Arg Thr Thr Trp Ala Ser Ser
660 665 670

Ser Ser Pro Asn Asp Arg Thr Phe Pro Asp Asp Arg Asn Phe Leu Arg
675 680 685

Leu Gln Ser Asp Ser Gln Arg Glu Gly Gln Tyr Ala Arg Leu Ile Ser
690 695 700

Pro Pro Val His Leu Pro Arg Ser Pro Val Cys Met Glu Phe Gln Tyr
705 710 715 720

Gln Ala Thr Gly Gly Arg Gly Val Ala Leu Gln Val Val Arg Glu Ala
725 730 735

Ser Gln Glu Ser Lys Leu Leu Trp Val Ile Arg Glu Asp Gln Gly Gly
740 745 750

Glu Trp Lys His Gly Arg Ile Ile Leu Pro Ser Tyr Asp Met Glu Tyr
755 760 765

Gln Ile Val Phe Glu Gly Val Ile Gly Lys Gly Arg Ser Gly Glu Ile
770 775 780

Ala Ile Asp Asp Ile Arg Ile Ser Thr Asp Val Pro Leu Glu Asn Cys
785 790 795 800

Met Glu Pro Ile Ser Ala Phe Ala Val Asp Ile Pro Glu Ile His Glu
805 810 815

Arg Glu Gly Tyr Glu Asp Glu Ile Asp Asp Glu Tyr Glu Val Asp Trp
820 825 830

Ser Asn Ser Ser Ser Ala Thr Ser Gly Ser Gly Ala Pro Ser Thr Asp
835 840 845

Lys Glu Lys Ser Trp Leu Tyr Thr Leu Asp Pro Ile Leu Ile Thr Ile
850 855 860

```
Ile Ala Met Ser Ser Leu Gly Val Leu Leu Gly Ala Thr Cys Ala Gly
865                 870                 875                 880

Leu Leu Leu Tyr Cys Thr Cys Ser Tyr Ser Gly Leu Ser Ser Arg Ser
                885                 890                 895

Cys Thr Thr Leu Glu Asn Tyr Asn Phe Glu Leu Tyr Asp Gly Leu Lys
            900                 905                 910

His Lys Val Lys Met Asn His Gln Lys Cys Cys Ser Glu Ala
        915                 920                 925


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<213>  Mus musculus


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<221>  misc_feature

<222>  (348)..(410)

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gctaaatgac aggatgcagg cgacttgaga cacaaaaaga gaagcgcttc tcgcgaattc     180

aggcattgcc tcgccgctag ccttccccgc caagacccgc tgaggatttt atggttctta     240

ggcggactta agagcgtttc ggattgttaa gattatcgtt tgctggtttt tcgtccgcgc     300

aatcgtgttc tcctgcggct gcctggggac tggcttggcg aaggagg atg gag agg       356
                                                    Met Glu Arg
                                                    1

ggg ctg ccg ttg ctg tgc gcc acg ctc gcc ctt gcc ctc gcc ctg gcg       404
Gly Leu Pro Leu Leu Cys Ala Thr Leu Ala Leu Ala Leu Ala Leu Ala
    5                   10                  15
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ggc gct ttc cgc agc gac aaa tgt ggc ggg acc ata aaa atc gaa aac      452
Gly Ala Phe Arg Ser Asp Lys Cys Gly Gly Thr Ile Lys Ile Glu Asn
20                  25                  30                  35

cca ggg tac ctc aca tct ccc ggt tac cct cat tct tac cat cca agt      500
Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr His Pro Ser
                40                  45                  50

gag aag tgt gaa tgg cta atc caa gct ccg gaa ccc tac cag aga atc      548
Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Glu Pro Tyr Gln Arg Ile
            55                  60                  65

ata atc aac ttc aac cca cat ttc gat ttg gag gac aga gac tgc aag      596
Ile Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg Asp Cys Lys
        70                  75                  80

tat gac tac gtg gaa gta att gat ggg gag aat gaa ggc ggc cgc ctg      644
Tyr Asp Tyr Val Glu Val Ile Asp Gly Glu Asn Glu Gly Gly Arg Leu
    85                  90                  95

tgg ggg aag ttc tgt ggg aag att gca cct tct cct gtg gtg tct tca      692
Trp Gly Lys Phe Cys Gly Lys Ile Ala Pro Ser Pro Val Val Ser Ser
100                 105                 110                 115

ggg ccc ttt ctc ttc atc aaa ttt gtc tct gac tat gag aca cat ggg      740
Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu Thr His Gly
                120                 125                 130

gca ggg ttt tcc atc cgc tat gaa atc ttc aag aga ggg ccc gaa tgt      788
Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly Pro Glu Cys
            135                 140                 145

tct cag aac tat aca gca cct act gga gtg ata aag tcc cct ggg ttc      836
Ser Gln Asn Tyr Thr Ala Pro Thr Gly Val Ile Lys Ser Pro Gly Phe
        150                 155                 160

cct gaa aaa tac ccc aac tgc ttg gag tgc acc tac atc atc ttt gca      884
Pro Glu Lys Tyr Pro Asn Cys Leu Glu Cys Thr Tyr Ile Ile Phe Ala
    165                 170                 175

cca aag atg tct gag ata atc ctg gag ttt gaa agt ttt gac ctg gag      932
Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe Asp Leu Glu
180                 185                 190                 195

caa gac tcg aat cct ccc gga gga atg ttc tgt cgc tat gac cgg ctg      980
Gln Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr Asp Arg Leu
                200                 205                 210

gag atc tgg gat gga ttc cct gaa gtt ggc cct cac att ggg cgt tat      1028
Glu Ile Trp Asp Gly Phe Pro Glu Val Gly Pro His Ile Gly Arg Tyr
            215                 220                 225

tgt ggg cag aaa act cct ggc cgg atc cgc tcc tct tca ggc gtt cta      1076
Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser Gly Val Leu
        230                 235                 240

tcc atg gtc ttt tac act gac agc gca ata gca aaa gaa ggt ttc tca      1124
Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu Gly Phe Ser
    245                 250                 255

gcc aac tac agt gtg cta cag agc agc atc tct gaa gat ttt aag tgt      1172
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Ala Asn Tyr Ser Val Leu Gln Ser Ser Ile Ser Glu Asp Phe Lys Cys
260 265 270 275

atg gag gct ctg ggc atg gaa tct gga gag atc cat tct gat cag atc 1220
Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser Asp Gln Ile
280 285 290

act gca tct tca cag tat ggt acc aac tgg tct gta gag cgc tcc cgc 1268
Thr Ala Ser Ser Gln Tyr Gly Thr Asn Trp Ser Val Glu Arg Ser Arg
295 300 305

ctg aac tac cct gaa aat ggg tgg act cca gga gaa gac tcc tac aag 1316
Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp Ser Tyr Lys
310 315 320

gag tgg atc cag gtg gac ttg ggc ctc ctg cga ttc gtt act gct gta 1364
Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val Thr Ala Val
325 330 335

ggg aca cag ggt gcc att tcc aag gaa acc aag aag aaa tat tat gtc 1412
Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys Tyr Tyr Val
340 345 350 355

aag act tac aga gta gac atc agc tcc aac gga gag gac tgg atc tcc 1460
Lys Thr Tyr Arg Val Asp Ile Ser Ser Asn Gly Glu Asp Trp Ile Ser
360 365 370

ctg aaa gag gga aat aaa gcc att atc ttt cag gga aac acc aac ccc 1508
Leu Lys Glu Gly Asn Lys Ala Ile Ile Phe Gln Gly Asn Thr Asn Pro
375 380 385

aca gat gtt gtc tta gga gtt ttc tcc aaa cca ctg ata act cga ttt 1556
Thr Asp Val Val Leu Gly Val Phe Ser Lys Pro Leu Ile Thr Arg Phe
390 395 400

gtc cga atc aaa cct gta tcc tgg gaa act ggt ata tct atg aga ttt 1604
Val Arg Ile Lys Pro Val Ser Trp Glu Thr Gly Ile Ser Met Arg Phe
405 410 415

gaa gtt tat ggc tgc aag ata aca gat tat cct tgc tct gga atg ttg 1652
Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser Gly Met Leu
420 425 430 435

ggc atg gtg tct gga ctt att tca gac tcc cag att aca gca tcc aat 1700
Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr Ala Ser Asn
440 445 450

caa gcc gac agg aat tgg atg cca gaa aac atc cgt ctg gtg acc agt 1748
Gln Ala Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu Val Thr Ser
455 460 465

cgt acc ggc tgg gca ctg cca ccc tca ccc cac cca tac acc aat gaa 1796
Arg Thr Gly Trp Ala Leu Pro Pro Ser Pro His Pro Tyr Thr Asn Glu
470 475 480

tgg ctc caa gtg gac ctg gga gat gag aag ata gta aga ggt gtc atc 1844
Trp Leu Gln Val Asp Leu Gly Asp Glu Lys Ile Val Arg Gly Val Ile
485 490 495

att cag ggt ggg aag cac cga gaa aac aag gtg ttc atg agg aag ttc 1892
Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met Arg Lys Phe

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500                 505                 510                 515

aag atc gcc tat agt aac aat ggc tct gac tgg aaa act atc atg gat      1940
Lys Ile Ala Tyr Ser Asn Asn Gly Ser Asp Trp Lys Thr Ile Met Asp
                520                 525                 530

gac agc aag cgc aag gct aag tcg ttc gaa ggc aac aac aac tat gac      1988
Asp Ser Lys Arg Lys Ala Lys Ser Phe Glu Gly Asn Asn Asn Tyr Asp
            535                 540                 545

aca cct gag ctt cgg acg ttt tca cct ctc tcc aca agg ttc atc agg      2036
Thr Pro Glu Leu Arg Thr Phe Ser Pro Leu Ser Thr Arg Phe Ile Arg
        550                 555                 560

atc tac cct gag aga gcc aca cac agt ggg ctt ggg ctg agg atg gag      2084
Ile Tyr Pro Glu Arg Ala Thr His Ser Gly Leu Gly Leu Arg Met Glu
    565                 570                 575

cta ctg ggc tgt gaa gtg gaa gca cct aca gct gga cca acc aca ccc      2132
Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro Thr Thr Pro
580                 585                 590                 595

aat ggg aac cca gtg cat gag tgt gac gac gac cag gcc aac tgc cac      2180
Asn Gly Asn Pro Val His Glu Cys Asp Asp Asp Gln Ala Asn Cys His
                600                 605                 610

agt ggc aca ggt gat gac ttc cag ctc aca gga ggc acc act gtc ctg      2228
Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr Thr Val Leu
            615                 620                 625

gcc aca gag aag cca acc att ata gac agc acc atc caa tca gag ttc      2276
Ala Thr Glu Lys Pro Thr Ile Ile Asp Ser Thr Ile Gln Ser Glu Phe
        630                 635                 640

ccg aca tac ggt ttt aac tgc gag ttt ggc tgg ggc tct cac aag aca      2324
Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser His Lys Thr
    645                 650                 655

ttc tgc cac tgg gag cat gac agc cat gca cag ctc agg tgg agt gtg      2372
Phe Cys His Trp Glu His Asp Ser His Ala Gln Leu Arg Trp Ser Val
660                 665                 670                 675

ctg acc agc aag aca ggg ccg att cag gac cat aca gga gat ggc aac      2420
Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly Asp Gly Asn
                680                 685                 690

ttc atc tat tcc caa gct gat gaa aat cag aaa ggc aaa gta gcc cgc      2468
Phe Ile Tyr Ser Gln Ala Asp Glu Asn Gln Lys Gly Lys Val Ala Arg
            695                 700                 705

ctg gtg agc cct gtg gtc tat tcc cag agc tct gcc cac tgt atg acc      2516
Leu Val Ser Pro Val Val Tyr Ser Gln Ser Ser Ala His Cys Met Thr
        710                 715                 720

ttc tgg tat cac atg tcc ggc tct cat gtg ggt aca ctg agg gtc aaa      2564
Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu Arg Val Lys
    725                 730                 735

cta cgc tac cag aag cca gag gaa tat gat caa ctg gtc tgg atg gtg      2612
Leu Arg Tyr Gln Lys Pro Glu Glu Tyr Asp Gln Leu Val Trp Met Val
740                 745                 750                 755
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gtt ggg cac caa gga gac cac tgg aaa gaa gga cgt gtc ttg ctg cac 2660
Val Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val Leu Leu His
760 765 770

aaa tct ctg aaa cta tat cag gtt att ttt gaa ggt gaa atc gga aaa 2708
Lys Ser Leu Lys Leu Tyr Gln Val Ile Phe Glu Gly Glu Ile Gly Lys
775 780 785

gga aac ctt ggt gga att gct gtg gat gat atc agt att aac aac cat 2756
Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile Asn Asn His
790 795 800

att tct cag gaa gac tgt gca aaa cca aca gac cta gat aaa aag aac 2804
Ile Ser Gln Glu Asp Cys Ala Lys Pro Thr Asp Leu Asp Lys Lys Asn
805 810 815

aca gaa att aaa att gat gaa aca ggg agc act cca gga tat gaa gga 2852
Thr Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly Tyr Glu Gly
820 825 830 835

gaa ggg gaa ggt gac aag aac atc tcc agg aag cca ggc aat gtg ctt 2900
Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly Asn Val Leu
840 845 850

aag acc ctg gat ccc atc ctg atc acc atc ata gcc atg agt gcc ctg 2948
Lys Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile Ala Met Ser Ala Leu
855 860 865

gga gta ctc ctg ggt gca gtc tgt gga gtt gtg ctg tac tgt gcc tgt 2996
Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr Cys Ala Cys
870 875 880

tgg cac aat ggg atg tca gaa agg aac cta tct gcc ctg gag aac tat 3044
Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu Glu Asn Tyr
885 890 895

aac ttt gaa ctt gtg gat ggt gta aag ttg aaa aaa gat aaa ctg aac 3092
Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp Lys Leu Asn
900 905 910 915

cca cag agt aat tac tca gag gcg tga aggcacggag ctggagggaa 3139
Pro Gln Ser Asn Tyr Ser Glu Ala
920

caagggagga gcacggcagg agaacaggtg gaggcatggg gactctgtta ctctgctttc 3199

actgtaagct gggaagggcg gggactctgt tactccgctt tcactgtaag ctcggaaggg 3259

catccacgat gccatgccag gcttttctca ggagcttcaa tgagcgtcac ctacagacac 3319

aagcaggtga ctgcggtaac aacaggaatc atgtacaagc ctgctttctt ctcttggttt 3379

catttgggta atcagaagcc atttgagacc aagtgtgact gacttcatgg ttcatcctac 3439

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aaatccaaga tgctggcact aggcgttatt cagtgggccc ttttgatgga catgtgacct 3559

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Ile Glu Asn Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr
35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Glu Pro Tyr
50 55 60

Gln Arg Ile Ile Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Ile Asp Gly Glu Asn Glu Gly
85 90 95

Gly Arg Leu Trp Gly Lys Phe Cys Gly Lys Ile Ala Pro Ser Pro Val
100 105 110

Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu
115 120 125

Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly
130 135 140

Pro Glu Cys Ser Gln Asn Tyr Thr Ala Pro Thr Gly Val Ile Lys Ser
145 150 155 160

Pro Gly Phe Pro Glu Lys Tyr Pro Asn Cys Leu Glu Cys Thr Tyr Ile
165 170 175

Ile Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe
180 185 190

Asp Leu Glu Gln Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr
195 200 205

Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Glu Val Gly Pro His Ile
210 215 220

Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser
225 230 235 240

Gly Val Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu
245 250 255

Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Ile Ser Glu Asp
260 265 270

Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser
275 280 285

Asp Gln Ile Thr Ala Ser Ser Gln Tyr Gly Thr Asn Trp Ser Val Glu
290 295 300

Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp
305 310 315 320

Ser Tyr Lys Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val
325 330 335

Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys
340 345 350

Tyr Tyr Val Lys Thr Tyr Arg Val Asp Ile Ser Ser Asn Gly Glu Asp
355 360 365

Trp Ile Ser Leu Lys Glu Gly Asn Lys Ala Ile Ile Phe Gln Gly Asn
370 375 380

Thr Asn Pro Thr Asp Val Val Leu Gly Val Phe Ser Lys Pro Leu Ile
385 390 395 400

Thr Arg Phe Val Arg Ile Lys Pro Val Ser Trp Glu Thr Gly Ile Ser
405 410 415

Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser
420 425 430

Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr
435 440 445

Ala Ser Asn Gln Ala Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu
450 455 460

Val Thr Ser Arg Thr Gly Trp Ala Leu Pro Pro Ser Pro His Pro Tyr
465 470 475 480

Thr Asn Glu Trp Leu Gln Val Asp Leu Gly Asp Glu Lys Ile Val Arg
485 490 495

Gly Val Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met
500 505 510

Arg Lys Phe Lys Ile Ala Tyr Ser Asn Asn Gly Ser Asp Trp Lys Thr
515 520 525

Ile Met Asp Asp Ser Lys Arg Lys Ala Lys Ser Phe Glu Gly Asn Asn
530 535 540

Asn Tyr Asp Thr Pro Glu Leu Arg Thr Phe Ser Pro Leu Ser Thr Arg
545 550 555 560

Phe Ile Arg Ile Tyr Pro Glu Arg Ala Thr His Ser Gly Leu Gly Leu
565 570 575

Arg Met Glu Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro
580 585 590

Thr Thr Pro Asn Gly Asn Pro Val His Glu Cys Asp Asp Asp Gln Ala
595 600 605

Asn Cys His Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr
610 615 620

Thr Val Leu Ala Thr Glu Lys Pro Thr Ile Ile Asp Ser Thr Ile Gln
625 630 635 640

Ser Glu Phe Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser
645 650 655

His Lys Thr Phe Cys His Trp Glu His Asp Ser His Ala Gln Leu Arg
660 665 670

Trp Ser Val Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly
675 680 685

Asp Gly Asn Phe Ile Tyr Ser Gln Ala Asp Glu Asn Gln Lys Gly Lys
    690   695   700

Val Ala Arg Leu Val Ser Pro Val Val Tyr Ser Gln Ser Ser Ala His
705   710   715   720

Cys Met Thr Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu
                725   730   735

Arg Val Lys Leu Arg Tyr Gln Lys Pro Glu Glu Tyr Asp Gln Leu Val
            740   745   750

Trp Met Val Val Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val
        755   760   765

Leu Leu His Lys Ser Leu Lys Leu Tyr Gln Val Ile Phe Glu Gly Glu
    770   775   780

Ile Gly Lys Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile
785   790   795   800

Asn Asn His Ile Ser Gln Glu Asp Cys Ala Lys Pro Thr Asp Leu Asp
                805   810   815

Lys Lys Asn Thr Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly
            820   825   830

Tyr Glu Gly Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly
        835   840   845

Asn Val Leu Lys Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile Ala Met
    850   855   860

Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr
865   870   875   880

Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu
                885   890   895

Glu Asn Tyr Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp
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Lys Leu Asn Pro Gln Ser Asn Tyr Ser Glu Ala
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tgtcagttag cgcttctgag atcacacagc tgcctagggg ccgtgtgatg cccagggcaa     180

ttcttggctt tgatttttat tattattact attattttgc gttcagcttt cgggaaaccc     240

tcgtgatgtt gtaggataaa ggaaatgaca ctttgaggaa ctggagagaa catacacgcg     300

tttgggtttg aagaggaaac cggtctccgc ttccttagct tgctccctct ttgctgattt     360

caagagctat ctcctatgag gtggagatat tccagcaaga ataaaggtga agacagactg     420

actgccagga cccaggagga aaacgttgat cgttagagac ctttgcagaa gacaccacca     480

ggaggaaaat tagagaggaa aaacacaaag acataattat aggagatccc acaaacctag     540

cccgggagag agcctctctg tcaaaa atg gat atg ttt cct ctt acc tgg gtt      593
                             Met Asp Met Phe Pro Leu Thr Trp Val
                             1               5

ttc tta gct ctg tac ttt tca gga cac gaa gtg aga agc cag caa gat       641
Phe Leu Ala Leu Tyr Phe Ser Gly His Glu Val Arg Ser Gln Gln Asp
10                  15                  20                  25

cca ccc tgc gga ggt cgg ccg aat tcc aaa gat gct ggc tac atc act       689
Pro Pro Cys Gly Gly Arg Pro Asn Ser Lys Asp Ala Gly Tyr Ile Thr
                30                  35                  40

tcc cca ggc tac ccc cag gac tat ccc tcc cac cag aac tgt gag tgg       737
Ser Pro Gly Tyr Pro Gln Asp Tyr Pro Ser His Gln Asn Cys Glu Trp
            45                  50                  55

att gtc tac gcc ccc gaa ccc aac cag aag att gtt ctc aac ttc aac       785
Ile Val Tyr Ala Pro Glu Pro Asn Gln Lys Ile Val Leu Asn Phe Asn
        60                  65                  70

cct cac ttt gaa atc gag aaa cac gac tgc aag tat gac ttc att gag       833
Pro His Phe Glu Ile Glu Lys His Asp Cys Lys Tyr Asp Phe Ile Glu
    75                  80                  85

att cgg gat ggg gac agt gag tca gct gac ctc ctg ggc aag cac tgt       881
Ile Arg Asp Gly Asp Ser Glu Ser Ala Asp Leu Leu Gly Lys His Cys
90                  95                  100                 105
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ggg aac atc gcc ccg ccc acc atc atc tcc tca ggc tcc gtg tta tac      929
Gly Asn Ile Ala Pro Pro Thr Ile Ile Ser Ser Gly Ser Val Leu Tyr
                110                 115                 120

atc aag ttc acc tca gac tac gcc cgg cag ggg gca ggt ttc tct cta      977
Ile Lys Phe Thr Ser Asp Tyr Ala Arg Gln Gly Ala Gly Phe Ser Leu
            125                 130                 135

cgc tat gag atc ttc aaa aca ggc tct gaa gat tgt tcc aag aac ttt     1025
Arg Tyr Glu Ile Phe Lys Thr Gly Ser Glu Asp Cys Ser Lys Asn Phe
        140                 145                 150

aca agc ccc aat ggg acc att gaa tct cca ggg ttt cca gag aag tat     1073
Thr Ser Pro Asn Gly Thr Ile Glu Ser Pro Gly Phe Pro Glu Lys Tyr
    155                 160                 165

cca cac aat ctg gac tgt acc ttc acc atc ctg gcc aaa ccc agg atg     1121
Pro His Asn Leu Asp Cys Thr Phe Thr Ile Leu Ala Lys Pro Arg Met
170                 175                 180                 185

gag atc atc cta cag ttc ctg acc ttt gac ctg gag cat gac cct cta     1169
Glu Ile Ile Leu Gln Phe Leu Thr Phe Asp Leu Glu His Asp Pro Leu
                190                 195                 200

caa gtg ggg gaa gga gac tgt aaa tat gac tgg ctg gac atc tgg gat     1217
Gln Val Gly Glu Gly Asp Cys Lys Tyr Asp Trp Leu Asp Ile Trp Asp
            205                 210                 215

ggc att cca cat gtt gga cct ctg att ggc aag tac tgt ggg acg aaa     1265
Gly Ile Pro His Val Gly Pro Leu Ile Gly Lys Tyr Cys Gly Thr Lys
        220                 225                 230

aca ccc tcc aaa ctc cgc tcg tcc acg ggg atc ctc tcc ttg acc ttt     1313
Thr Pro Ser Lys Leu Arg Ser Ser Thr Gly Ile Leu Ser Leu Thr Phe
    235                 240                 245

cac acg gac atg gca gtg gcc aag gat ggc ttc tcc gca cgt tac tat     1361
His Thr Asp Met Ala Val Ala Lys Asp Gly Phe Ser Ala Arg Tyr Tyr
250                 255                 260                 265

ttg atc cac cag gag cca cct gag aat ttt cag tgc aat gtc cct ttg     1409
Leu Ile His Gln Glu Pro Pro Glu Asn Phe Gln Cys Asn Val Pro Leu
                270                 275                 280

gga atg gag tct ggc cgg att gct aat gaa cag atc agt gcc tcc tcc     1457
Gly Met Glu Ser Gly Arg Ile Ala Asn Glu Gln Ile Ser Ala Ser Ser
            285                 290                 295

acc ttc tct gat ggg agg tgg act cct caa cag agc cgg ctc cat ggt     1505
Thr Phe Ser Asp Gly Arg Trp Thr Pro Gln Gln Ser Arg Leu His Gly
        300                 305                 310

gat gac aat ggc tgg aca ccc aat ttg gat tcc aac aag gag tat ctc     1553
Asp Asp Asn Gly Trp Thr Pro Asn Leu Asp Ser Asn Lys Glu Tyr Leu
    315                 320                 325

cag gtg gac ctg cgc ttc cta acc atg ctc aca gcc att gca aca cag     1601
Gln Val Asp Leu Arg Phe Leu Thr Met Leu Thr Ala Ile Ala Thr Gln
330                 335                 340                 345

gga gcc att tcc agg gaa acc cag aaa ggc tac tac gtc aaa tcg tac     1649
Gly Ala Ile Ser Arg Glu Thr Gln Lys Gly Tyr Tyr Val Lys Ser Tyr
                350                 355                 360
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aag ctg gaa gtc agc aca aat ggt gaa gat tgg atg gtc tac cgg cat      1697
Lys Leu Glu Val Ser Thr Asn Gly Glu Asp Trp Met Val Tyr Arg His
            365                 370                 375

ggc aaa aac cac aag ata ttc caa gcg aac aat gat gcg acc gag gtg      1745
Gly Lys Asn His Lys Ile Phe Gln Ala Asn Asn Asp Ala Thr Glu Val
        380                 385                 390

gtg cta aac aag ctc cac atg cca ctg ctg act cgg ttc atc agg atc      1793
Val Leu Asn Lys Leu His Met Pro Leu Leu Thr Arg Phe Ile Arg Ile
    395                 400                 405

cgc ccg cag acg tgg cat ttg ggc att gcc ctt cgc ctg gag ctc ttt      1841
Arg Pro Gln Thr Trp His Leu Gly Ile Ala Leu Arg Leu Glu Leu Phe
410                 415                 420                 425

ggc tgc cgg gtc aca gat gca ccc tgc tcc aac atg ctg ggg atg ctc      1889
Gly Cys Arg Val Thr Asp Ala Pro Cys Ser Asn Met Leu Gly Met Leu
                430                 435                 440

tcg ggc ctc att gct gat acc cag atc tct gcc tcc tcc acc cga gag      1937
Ser Gly Leu Ile Ala Asp Thr Gln Ile Ser Ala Ser Ser Thr Arg Glu
            445                 450                 455

tac ctc tgg agc ccc agt gct gcc cgc ctg gtt agt agc cgc tct ggc      1985
Tyr Leu Trp Ser Pro Ser Ala Ala Arg Leu Val Ser Ser Arg Ser Gly
        460                 465                 470

tgg ttt cct cgg aac cct caa gcc cag cca ggt gaa gaa tgg ctt cag      2033
Trp Phe Pro Arg Asn Pro Gln Ala Gln Pro Gly Glu Glu Trp Leu Gln
    475                 480                 485

gta gac ctg ggg aca ccc aag aca gtg aaa ggg gtc atc atc cag gga      2081
Val Asp Leu Gly Thr Pro Lys Thr Val Lys Gly Val Ile Ile Gln Gly
490                 495                 500                 505

gcc cga gga gga gac agc atc act gcc gtg gaa gcc agg gcg ttt gta      2129
Ala Arg Gly Gly Asp Ser Ile Thr Ala Val Glu Ala Arg Ala Phe Val
                510                 515                 520

cgc aag ttc aaa gtc tcc tac agc cta aat ggc aag gac tgg gaa tat      2177
Arg Lys Phe Lys Val Ser Tyr Ser Leu Asn Gly Lys Asp Trp Glu Tyr
            525                 530                 535

atc cag gac ccc agg act cag cag aca aag ctg ttt gaa ggg aac atg      2225
Ile Gln Asp Pro Arg Thr Gln Gln Thr Lys Leu Phe Glu Gly Asn Met
        540                 545                 550

cac tat gac acc cct gac atc cga agg ttc gat cct gtt cca gcg cag      2273
His Tyr Asp Thr Pro Asp Ile Arg Arg Phe Asp Pro Val Pro Ala Gln
    555                 560                 565

tat gtg cgg gtg tac cca gag agg tgg tcg cca gca ggc atc ggg atg      2321
Tyr Val Arg Val Tyr Pro Glu Arg Trp Ser Pro Ala Gly Ile Gly Met
570                 575                 580                 585

agg ctg gag gtg ctg ggc tgt gac tgg aca gac tca aag ccc aca gtg      2369
Arg Leu Glu Val Leu Gly Cys Asp Trp Thr Asp Ser Lys Pro Thr Val
                590                 595                 600

gag acg ctg gga ccc acc gtg aag agt gaa gag act acc acc cca tat      2417
Glu Thr Leu Gly Pro Thr Val Lys Ser Glu Glu Thr Thr Thr Pro Tyr
            605                 610                 615
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ccc atg gat gag gat gcc acc gag tgt ggg gaa aac tgc agc ttt gag 2465
Pro Met Asp Glu Asp Ala Thr Glu Cys Gly Glu Asn Cys Ser Phe Glu
620 625 630

gat gac aaa gat ttg caa ctt cct tca gga ttc aac tgc aac ttt gat 2513
Asp Asp Lys Asp Leu Gln Leu Pro Ser Gly Phe Asn Cys Asn Phe Asp
635 640 645

ttt ccg gaa gag acc tgt ggt tgg gtg tac gac cat gcc aag tgg ctc 2561
Phe Pro Glu Glu Thr Cys Gly Trp Val Tyr Asp His Ala Lys Trp Leu
650 655 660 665

cgg agc acg tgg atc agc agc gct aac ccc aat gac aga aca ttt cca 2609
Arg Ser Thr Trp Ile Ser Ser Ala Asn Pro Asn Asp Arg Thr Phe Pro
670 675 680

gat gac aag aac ttc ttg aaa ctg cag agt gat ggc cga cga gag ggc 2657
Asp Asp Lys Asn Phe Leu Lys Leu Gln Ser Asp Gly Arg Arg Glu Gly
685 690 695

cag tac ggg cgg ctc atc agc cca ccg gtg cac ctg ccc cga agc cct 2705
Gln Tyr Gly Arg Leu Ile Ser Pro Pro Val His Leu Pro Arg Ser Pro
700 705 710

gtg tgc atg gag ttc cag tac caa gcc atg ggc ggc cac ggg gtg gca 2753
Val Cys Met Glu Phe Gln Tyr Gln Ala Met Gly Gly His Gly Val Ala
715 720 725

ctg cag gtg gtt cgg gaa gcc agc cag gaa agc aaa ctc ctt tgg gtc 2801
Leu Gln Val Val Arg Glu Ala Ser Gln Glu Ser Lys Leu Leu Trp Val
730 735 740 745

atc cgt gag gac cag ggc agc gag tgg aag cac ggg cgc att atc ctg 2849
Ile Arg Glu Asp Gln Gly Ser Glu Trp Lys His Gly Arg Ile Ile Leu
750 755 760

ccc agc tat gac atg gag tat cag atc gtg ttc gag gga gtg ata ggg 2897
Pro Ser Tyr Asp Met Glu Tyr Gln Ile Val Phe Glu Gly Val Ile Gly
765 770 775

aag gga cga tcg gga gag att tcc ggc gat gac att cgg ata agc act 2945
Lys Gly Arg Ser Gly Glu Ile Ser Gly Asp Asp Ile Arg Ile Ser Thr
780 785 790

gat gtc cca ctg gag aac tgc atg gaa ccc ata tca gct ttt gca gat 2993
Asp Val Pro Leu Glu Asn Cys Met Glu Pro Ile Ser Ala Phe Ala Asp
795 800 805

gaa tat gaa gga gat tgg agc aac tct tct tcc tct acc tca ggg gct 3041
Glu Tyr Glu Gly Asp Trp Ser Asn Ser Ser Ser Ser Thr Ser Gly Ala
810 815 820 825

ggt gac ccc tca tct ggc aaa gaa aag agc tgg ctg tac acc cta gat 3089
Gly Asp Pro Ser Ser Gly Lys Glu Lys Ser Trp Leu Tyr Thr Leu Asp
830 835 840

ccc att ctg atc acc atc atc gcc atg agc tcg ctg ggg gtc ctg ctg 3137
Pro Ile Leu Ile Thr Ile Ile Ala Met Ser Ser Leu Gly Val Leu Leu
845 850 855

ggg gcc acc tgt gcg ggc ctc ctc ctt tac tgc acc tgc tcc tat tcg 3185
Gly Ala Thr Cys Ala Gly Leu Leu Leu Tyr Cys Thr Cys Ser Tyr Ser
860 865 870

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ggt ctg agt tcg agg agc tgc acc aca ctg gag aac tac aac ttt gag      3233
Gly Leu Ser Ser Arg Ser Cys Thr Thr Leu Glu Asn Tyr Asn Phe Glu
    875                 880                 885

ctc tac gat ggc ctc aag cac aag gtc aag atc aat cat cag aag tgc      3281
Leu Tyr Asp Gly Leu Lys His Lys Val Lys Ile Asn His Gln Lys Cys
890                 895                 900                 905

tgc tcg gag gca tga ccgattgtgt ctggatcgct tctggcgttt cattccagtg      3336
Cys Ser Glu Ala

agaggggcta gcgaagatta cagttttgtt ttgttttgtt ttgttttccc tttggaaact   3396

gaatgccata atctggatca aagtgttcca gaatactgaa ggtatggaca ggacagacag   3456

gccagtctag ggagaaaggg agatgcagct gtgaagggga tcgttgccca ccaggactgt   3516

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tgcctctgga aaggctcaac catactcagt gccaactcag actctgttgc tgtggtgtca   3636

acatggatgg atcatctgta ccttgtattt ttagcagaat tcatgctcag atttctttgt   3696

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gtgcagatcc atgactgggg ctagtgcagc aatgaaacag aattccagaa acagtgtgtt   3876

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tgtgtgtgtt tgtctgtgta cctctttgta taagtacctg tgtttgtatg tgggaatatg   4476

tatattgagg cattgctgtg ttagtatgtt tatagaaaag aagacagtct gagatgtctt   4536

cctcaatacc tctccactta tatcttggat agacaaaagt aatgacaaaa aattgctggt   4596

gtgtatatgg aaaaggggga cacatatcca tggatggtag aagtgtaaac tgtgcagtca   4656

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35 40 45

Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro
50 55 60

Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys
65 70 75 80

His Asp Cys Lys Tyr Asp Phe Ile Glu Ile Arg Asp Gly Asp Ser Glu
85 90 95

Ser Ala Asp Leu Leu Gly Lys His Cys Gly Asn Ile Ala Pro Pro Thr
100 105 110

Ile Ile Ser Ser Gly Ser Val Leu Tyr Ile Lys Phe Thr Ser Asp Tyr
115 120 125

Ala Arg Gln Gly Ala Gly Phe Ser Leu Arg Tyr Glu Ile Phe Lys Thr
130 135 140

Gly Ser Glu Asp Cys Ser Lys Asn Phe Thr Ser Pro Asn Gly Thr Ile
145 150 155 160

Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr
165 170 175

Phe Thr Ile Leu Ala Lys Pro Arg Met Glu Ile Ile Leu Gln Phe Leu
180 185 190

Thr Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys
195 200 205

Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro

210 215 220

Leu Ile Gly Lys Tyr Cys Gly Thr Lys Thr Pro Ser Lys Leu Arg Ser
225 230 235 240

Ser Thr Gly Ile Leu Ser Leu Thr Phe His Thr Asp Met Ala Val Ala
245 250 255

Lys Asp Gly Phe Ser Ala Arg Tyr Tyr Leu Ile His Gln Glu Pro Pro
260 265 270

Glu Asn Phe Gln Cys Asn Val Pro Leu Gly Met Glu Ser Gly Arg Ile
275 280 285

Ala Asn Glu Gln Ile Ser Ala Ser Ser Thr Phe Ser Asp Gly Arg Trp
290 295 300

Thr Pro Gln Gln Ser Arg Leu His Gly Asp Asp Asn Gly Trp Thr Pro
305 310 315 320

Asn Leu Asp Ser Asn Lys Glu Tyr Leu Gln Val Asp Leu Arg Phe Leu
325 330 335

Thr Met Leu Thr Ala Ile Ala Thr Gln Gly Ala Ile Ser Arg Glu Thr
340 345 350

Gln Lys Gly Tyr Tyr Val Lys Ser Tyr Lys Leu Glu Val Ser Thr Asn
355 360 365

Gly Glu Asp Trp Met Val Tyr Arg His Gly Lys Asn His Lys Ile Phe
370 375 380

Gln Ala Asn Asn Asp Ala Thr Glu Val Val Leu Asn Lys Leu His Met
385 390 395 400

Pro Leu Leu Thr Arg Phe Ile Arg Ile Arg Pro Gln Thr Trp His Leu
405 410 415

Gly Ile Ala Leu Arg Leu Glu Leu Phe Gly Cys Arg Val Thr Asp Ala
420 425 430

Pro Cys Ser Asn Met Leu Gly Met Leu Ser Gly Leu Ile Ala Asp Thr
435 440 445

Gln Ile Ser Ala Ser Ser Thr Arg Glu Tyr Leu Trp Ser Pro Ser Ala
450 455 460

Ala Arg Leu Val Ser Ser Arg Ser Gly Trp Phe Pro Arg Asn Pro Gln
465 470 475 480

Ala Gln Pro Gly Glu Glu Trp Leu Gln Val Asp Leu Gly Thr Pro Lys
485 490 495

Thr Val Lys Gly Val Ile Ile Gln Gly Ala Arg Gly Gly Asp Ser Ile
500 505 510

Thr Ala Val Glu Ala Arg Ala Phe Val Arg Lys Phe Lys Val Ser Tyr
515 520 525

Ser Leu Asn Gly Lys Asp Trp Glu Tyr Ile Gln Asp Pro Arg Thr Gln
530 535 540

Gln Thr Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile
545 550 555 560

Arg Arg Phe Asp Pro Val Pro Ala Gln Tyr Val Arg Val Tyr Pro Glu
565 570 575

Arg Trp Ser Pro Ala Gly Ile Gly Met Arg Leu Glu Val Leu Gly Cys
580 585 590

Asp Trp Thr Asp Ser Lys Pro Thr Val Glu Thr Leu Gly Pro Thr Val
595 600 605

Lys Ser Glu Glu Thr Thr Thr Pro Tyr Pro Met Asp Glu Asp Ala Thr
610 615 620

Glu Cys Gly Glu Asn Cys Ser Phe Glu Asp Asp Lys Asp Leu Gln Leu
625 630 635 640

Pro Ser Gly Phe Asn Cys Asn Phe Asp Phe Pro Glu Glu Thr Cys Gly
645 650 655

Trp Val Tyr Asp His Ala Lys Trp Leu Arg Ser Thr Trp Ile Ser Ser
660 665 670

Ala Asn Pro Asn Asp Arg Thr Phe Pro Asp Asp Lys Asn Phe Leu Lys
675 680 685

Leu Gln Ser Asp Gly Arg Arg Glu Gly Gln Tyr Gly Arg Leu Ile Ser
690 695 700

Pro Pro Val His Leu Pro Arg Ser Pro Val Cys Met Glu Phe Gln Tyr
705 710 715 720

Gln Ala Met Gly Gly His Gly Val Ala Leu Gln Val Val Arg Glu Ala
725 730 735

Ser Gln Glu Ser Lys Leu Leu Trp Val Ile Arg Glu Asp Gln Gly Ser
740 745 750

Glu Trp Lys His Gly Arg Ile Ile Leu Pro Ser Tyr Asp Met Glu Tyr
755 760 765

Gln Ile Val Phe Glu Gly Val Ile Gly Lys Gly Arg Ser Gly Glu Ile
770 775 780

Ser Gly Asp Asp Ile Arg Ile Ser Thr Asp Val Pro Leu Glu Asn Cys
785 790 795 800

Met Glu Pro Ile Ser Ala Phe Ala Asp Glu Tyr Glu Gly Asp Trp Ser
805 810 815

Asn Ser Ser Ser Ser Thr Ser Gly Ala Gly Asp Pro Ser Ser Gly Lys
820 825 830

Glu Lys Ser Trp Leu Tyr Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile
835 840 845

Ala Met Ser Ser Leu Gly Val Leu Leu Gly Ala Thr Cys Ala Gly Leu
850 855 860

Leu Leu Tyr Cys Thr Cys Ser Tyr Ser Gly Leu Ser Ser Arg Ser Cys
865 870 875 880

Thr Thr Leu Glu Asn Tyr Asn Phe Glu Leu Tyr Asp Gly Leu Lys His
885 890 895

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gga gta tta ctt aca gca aga gca aac tat cag aat ggg aag aac aat       99
Gly Val Leu Leu Thr Ala Arg Ala Asn Tyr Gln Asn Gly Lys Asn Asn
        15                  20                  25

gtg cca agg ctg aaa tta tcc tac aaa gaa atg ttg gaa tcc aac aat      147
Val Pro Arg Leu Lys Leu Ser Tyr Lys Glu Met Leu Glu Ser Asn Asn
    30                  35                  40

gtg atc act ttc aat ggc ttg gcc aac agc tcc agt tat cat acc ttc      195
Val Ile Thr Phe Asn Gly Leu Ala Asn Ser Ser Ser Tyr His Thr Phe
45                  50                  55                  60

ctt ttg gat gag gaa cgg agt agg ctg tat gtt gga gca aag gat cac      243
Leu Leu Asp Glu Glu Arg Ser Arg Leu Tyr Val Gly Ala Lys Asp His
                65                  70                  75

ata ttt tca ttc gac ctg gtt aat atc aag gat ttt caa aag att gtg      291
Ile Phe Ser Phe Asp Leu Val Asn Ile Lys Asp Phe Gln Lys Ile Val
            80                  85                  90


tgg cca gta tct tac acc aga aga gat gaa tgc aag tgg gct gga aaa      339
Trp Pro Val Ser Tyr Thr Arg Arg Asp Glu Cys Lys Trp Ala Gly Lys
        95                  100                 105

gac atc ctg aaa gaa tgt gct aat ttc atc aag gta ctt aag gca tat      387
Asp Ile Leu Lys Glu Cys Ala Asn Phe Ile Lys Val Leu Lys Ala Tyr
    110                 115                 120

aat cag act cac ttg tac gcc tgt gga acg ggg gct ttt cat cca att      435
Asn Gln Thr His Leu Tyr Ala Cys Gly Thr Gly Ala Phe His Pro Ile
125                 130                 135                 140

tgc acc tac att gaa att gga cat cat cct gag gac aat att ttt aag      483
Cys Thr Tyr Ile Glu Ile Gly His His Pro Glu Asp Asn Ile Phe Lys
                145                 150                 155

ctg gag aac tca cat ttt gaa aac ggc cgt ggg aag agt cca tat gac      531
Leu Glu Asn Ser His Phe Glu Asn Gly Arg Gly Lys Ser Pro Tyr Asp
            160                 165                 170

cct aag ctg ctg aca gca tcc ctt tta ata gat gga gaa tta tac tct      579
Pro Lys Leu Leu Thr Ala Ser Leu Leu Ile Asp Gly Glu Leu Tyr Ser
        175                 180                 185

gga act gca gct gat ttt atg ggg cga gac ttt gct atc ttc cga act      627
Gly Thr Ala Ala Asp Phe Met Gly Arg Asp Phe Ala Ile Phe Arg Thr
    190                 195                 200

ctt ggg cac cac cac cca atc agg aca gag cag cat gat tcc agg tgg      675
Leu Gly His His His Pro Ile Arg Thr Glu Gln His Asp Ser Arg Trp
205                 210                 215                 220
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ctc aat gat cca aag ttc att agt gcc cac ctc atc tca gag agt gac        723
Leu Asn Asp Pro Lys Phe Ile Ser Ala His Leu Ile Ser Glu Ser Asp
                225                 230                 235

aat cct gaa gat gac aaa gta tac ttt ttc ttc cgt gaa aat gca ata        771
Asn Pro Glu Asp Asp Lys Val Tyr Phe Phe Phe Arg Glu Asn Ala Ile
            240                 245                 250

gat gga gaa cac tct gga aaa gct act cac gct aga ata ggt cag ata        819
Asp Gly Glu His Ser Gly Lys Ala Thr His Ala Arg Ile Gly Gln Ile
        255                 260                 265

tgc aag aat gac ttt gga ggg cac aga agt ctg gtg aat aaa tgg aca        867
Cys Lys Asn Asp Phe Gly Gly His Arg Ser Leu Val Asn Lys Trp Thr
    270                 275                 280

aca ttc ctc aaa gct cgt ctg att tgc tca gtg cca ggt cca aat ggc        915
Thr Phe Leu Lys Ala Arg Leu Ile Cys Ser Val Pro Gly Pro Asn Gly
285                 290                 295                 300

att gac act cat ttt gat gaa ctg cag gat gta ttc cta atg aac ttt        963
Ile Asp Thr His Phe Asp Glu Leu Gln Asp Val Phe Leu Met Asn Phe
                305                 310                 315

aaa gat cct aaa aat cca gtt gta tat gga gtg ttt acg act tcc agt       1011
Lys Asp Pro Lys Asn Pro Val Val Tyr Gly Val Phe Thr Thr Ser Ser
            320                 325                 330

aac att ttc aag gga tca gcc gtg tgt atg tat agc atg agt gat gtg       1059
Asn Ile Phe Lys Gly Ser Ala Val Cys Met Tyr Ser Met Ser Asp Val
        335                 340                 345

aga agg gtg ttc ctt ggt cca tat gcc cac agg gat gga ccc aac tat       1107
Arg Arg Val Phe Leu Gly Pro Tyr Ala His Arg Asp Gly Pro Asn Tyr
    350                 355                 360

caa tgg gtg cct tat caa gga aga gtc ccc tat cca cgg cca gga act       1155
Gln Trp Val Pro Tyr Gln Gly Arg Val Pro Tyr Pro Arg Pro Gly Thr
365                 370                 375                 380

tgt ccc agc aaa aca ttt ggt ggt ttt gac tct aca aag gac ctt cct       1203
Cys Pro Ser Lys Thr Phe Gly Gly Phe Asp Ser Thr Lys Asp Leu Pro
                385                 390                 395

gat gat gtt ata acc ttt gca aga agt cat cca gcc atg tac aat cca       1251
Asp Asp Val Ile Thr Phe Ala Arg Ser His Pro Ala Met Tyr Asn Pro
            400                 405                 410

gtg ttt cct atg aac aat cgc cca ata gtg atc aaa acg gat gta aat       1299
Val Phe Pro Met Asn Asn Arg Pro Ile Val Ile Lys Thr Asp Val Asn
        415                 420                 425

tat caa ttt aca caa att gtc gta gac cga gtg gat gca gaa gat gga       1347
Tyr Gln Phe Thr Gln Ile Val Val Asp Arg Val Asp Ala Glu Asp Gly
    430                 435                 440

cag tat gat gtt atg ttt atc gga aca gat gtt ggg acc gtt ctt aaa       1395
Gln Tyr Asp Val Met Phe Ile Gly Thr Asp Val Gly Thr Val Leu Lys
445                 450                 455                 460

gta gtt tca att cct aag gag act tgg tat gat tta gaa gag gtt ctg       1443
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Val Val Ser Ile Pro Lys Glu Thr Trp Tyr Asp Leu Glu Glu Val Leu
                465                 470                 475

ctg gaa gaa atg aca gtt ttt cgg gaa ccg act gct att tca gca atg      1491
Leu Glu Glu Met Thr Val Phe Arg Glu Pro Thr Ala Ile Ser Ala Met
            480                 485                 490

gag ctt tcc act aag cag caa caa cta tat att ggt tca acg gct ggg      1539
Glu Leu Ser Thr Lys Gln Gln Gln Leu Tyr Ile Gly Ser Thr Ala Gly
        495                 500                 505

gtt gcc cag ctc cct tta cac cgg tgt gat att tac ggg aaa gcg tgt      1587
Val Ala Gln Leu Pro Leu His Arg Cys Asp Ile Tyr Gly Lys Ala Cys
    510                 515                 520

gct gag tgt tgc ctc gcc cga gac cct tac tgt gct tgg gat ggt tct      1635
Ala Glu Cys Cys Leu Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Ser
525                 530                 535                 540

gca tgt tct cgc tat ttt ccc act gca aag aga cgc aca aga cga caa      1683
Ala Cys Ser Arg Tyr Phe Pro Thr Ala Lys Arg Arg Thr Arg Arg Gln
                545                 550                 555

gat ata aga aat gga gac cca ctg act cac tgt tca gac tta cac cat      1731
Asp Ile Arg Asn Gly Asp Pro Leu Thr His Cys Ser Asp Leu His His
            560                 565                 570

gat aat cac cat ggc cac agc cct gaa gag aga atc atc tat ggt gta      1779
Asp Asn His His Gly His Ser Pro Glu Glu Arg Ile Ile Tyr Gly Val
        575                 580                 585

gag aat agt agc aca ttt ttg gaa tgc agt ccg aag tcg cag aga gcg      1827
Glu Asn Ser Ser Thr Phe Leu Glu Cys Ser Pro Lys Ser Gln Arg Ala
    590                 595                 600


ctg gtc tat tgg caa ttc cag agg cga aat gaa gag cga aaa gaa gag      1875
Leu Val Tyr Trp Gln Phe Gln Arg Arg Asn Glu Glu Arg Lys Glu Glu
605                 610                 615                 620

atc aga gtg gat gat cat atc atc agg aca gat caa ggc ctt ctg cta      1923
Ile Arg Val Asp Asp His Ile Ile Arg Thr Asp Gln Gly Leu Leu Leu
                625                 630                 635

cgt agt cta caa cag aag gat tca ggc aat tac ctc tgc cat gcg gtg      1971
Arg Ser Leu Gln Gln Lys Asp Ser Gly Asn Tyr Leu Cys His Ala Val
            640                 645                 650

gaa cat ggg ttc ata caa act ctt ctt aag gta acc ctg gaa gtc att      2019
Glu His Gly Phe Ile Gln Thr Leu Leu Lys Val Thr Leu Glu Val Ile
        655                 660                 665

gac aca gag cat ttg gaa gaa ctt ctt cat aaa gat gat gat gga gat      2067
Asp Thr Glu His Leu Glu Glu Leu Leu His Lys Asp Asp Asp Gly Asp
    670                 675                 680

ggc tct aag acc aaa gaa atg tcc aat agc atg aca cct agc cag aag      2115
Gly Ser Lys Thr Lys Glu Met Ser Asn Ser Met Thr Pro Ser Gln Lys
685                 690                 695                 700

gtc tgg tac aga gac ttc atg cag ctc atc aac cac ccc aat ctc aac      2163
Val Trp Tyr Arg Asp Phe Met Gln Leu Ile Asn His Pro Asn Leu Asn
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705 710 715

acg atg gat gag ttc tgt gaa caa gtt tgg aaa agg gac cga aaa caa 2211
Thr Met Asp Glu Phe Cys Glu Gln Val Trp Lys Arg Asp Arg Lys Gln
720 725 730

cgt cgg caa agg cca gga cat acc cca ggg aac agt aac aaa tgg aag 2259
Arg Arg Gln Arg Pro Gly His Thr Pro Gly Asn Ser Asn Lys Trp Lys
735 740 745

cac tta caa gaa aat aag aaa ggt aga aac agg agg acc cac gaa ttt 2307
His Leu Gln Glu Asn Lys Lys Gly Arg Asn Arg Arg Thr His Glu Phe
750 755 760

gag agg gca ccc agg agt gtc tga gctgcattac ctctagaaac ctcaaacaag 2361
Glu Arg Ala Pro Arg Ser Val
765 770

tagaaacttg cctagacaat aactggaaaa acaaatgcaa tatacatgaa ctttttttcat 2421

ggcattatgt ggatgtttac aatggtggga aattcagctg agttccacca attataaatt 2481

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Lys Leu Ser Tyr Lys Glu Met Leu Glu Ser Asn Asn Val Ile Thr Phe
35 40 45

Asn Gly Leu Ala Asn Ser Ser Ser Tyr His Thr Phe Leu Leu Asp Glu
50 55 60

Glu Arg Ser Arg Leu Tyr Val Gly Ala Lys Asp His Ile Phe Ser Phe
65 70 75 80

Asp Leu Val Asn Ile Lys Asp Phe Gln Lys Ile Val Trp Pro Val Ser
85 90 95

Tyr Thr Arg Arg Asp Glu Cys Lys Trp Ala Gly Lys Asp Ile Leu Lys
100 105 110

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Glu Cys Ala Asn Phe Ile Lys Val Leu Lys Ala Tyr Asn Gln Thr His
        115                 120                 125

Leu Tyr Ala Cys Gly Thr Gly Ala Phe His Pro Ile Cys Thr Tyr Ile
    130                 135                 140

Glu Ile Gly His His Pro Glu Asp Asn Ile Phe Lys Leu Glu Asn Ser
145                 150                 155                 160

His Phe Glu Asn Gly Arg Gly Lys Ser Pro Tyr Asp Pro Lys Leu Leu
                165                 170                 175

Thr Ala Ser Leu Leu Ile Asp Gly Glu Leu Tyr Ser Gly Thr Ala Ala
            180                 185                 190

Asp Phe Met Gly Arg Asp Phe Ala Ile Phe Arg Thr Leu Gly His His
        195                 200                 205

His Pro Ile Arg Thr Glu Gln His Asp Ser Arg Trp Leu Asn Asp Pro
    210                 215                 220

Lys Phe Ile Ser Ala His Leu Ile Ser Glu Ser Asp Asn Pro Glu Asp
225                 230                 235                 240

Asp Lys Val Tyr Phe Phe Phe Arg Glu Asn Ala Ile Asp Gly Glu His
                245                 250                 255

Ser Gly Lys Ala Thr His Ala Arg Ile Gly Gln Ile Cys Lys Asn Asp
            260                 265                 270

Phe Gly Gly His Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys
        275                 280                 285

Ala Arg Leu Ile Cys Ser Val Pro Gly Pro Asn Gly Ile Asp Thr His
    290                 295                 300

Phe Asp Glu Leu Gln Asp Val Phe Leu Met Asn Phe Lys Asp Pro Lys
305                 310                 315                 320

Asn Pro Val Val Tyr Gly Val Phe Thr Thr Ser Ser Asn Ile Phe Lys
                325                 330                 335

Gly Ser Ala Val Cys Met Tyr Ser Met Ser Asp Val Arg Arg Val Phe
            340                 345                 350

Leu Gly Pro Tyr Ala His Arg Asp Gly Pro Asn Tyr Gln Trp Val Pro
        355                 360                 365
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Tyr Gln Gly Arg Val Pro Tyr Pro Arg Pro Gly Thr Cys Pro Ser Lys
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Thr Phe Gly Gly Phe Asp Ser Thr Lys Asp Leu Pro Asp Asp Val Ile
385                 390                 395                 400

Thr Phe Ala Arg Ser His Pro Ala Met Tyr Asn Pro Val Phe Pro Met
                405                 410                 415

Asn Asn Arg Pro Ile Val Ile Lys Thr Asp Val Asn Tyr Gln Phe Thr
            420                 425                 430

Gln Ile Val Val Asp Arg Val Asp Ala Glu Asp Gly Gln Tyr Asp Val
        435                 440                 445

Met Phe Ile Gly Thr Asp Val Gly Thr Val Leu Lys Val Val Ser Ile
    450                 455                 460

Pro Lys Glu Thr Trp Tyr Asp Leu Glu Glu Val Leu Leu Glu Glu Met
465                 470                 475                 480

Thr Val Phe Arg Glu Pro Thr Ala Ile Ser Ala Met Glu Leu Ser Thr
                485                 490                 495

Lys Gln Gln Gln Leu Tyr Ile Gly Ser Thr Ala Gly Val Ala Gln Leu
            500                 505                 510

Pro Leu His Arg Cys Asp Ile Tyr Gly Lys Ala Cys Ala Glu Cys Cys
        515                 520                 525

Leu Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Ser Ala Cys Ser Arg
    530                 535                 540

Tyr Phe Pro Thr Ala Lys Arg Arg Thr Arg Arg Gln Asp Ile Arg Asn
545                 550                 555                 560

Gly Asp Pro Leu Thr His Cys Ser Asp Leu His His Asp Asn His His
                565                 570                 575

Gly His Ser Pro Glu Glu Arg Ile Ile Tyr Gly Val Glu Asn Ser Ser
            580                 585                 590

Thr Phe Leu Glu Cys Ser Pro Lys Ser Gln Arg Ala Leu Val Tyr Trp
        595                 600                 605

Gln Phe Gln Arg Arg Asn Glu Glu Arg Lys Glu Glu Ile Arg Val Asp
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610 615 620

Asp His Ile Ile Arg Thr Asp Gln Gly Leu Leu Leu Arg Ser Leu Gln
625 630 635 640

Gln Lys Asp Ser Gly Asn Tyr Leu Cys His Ala Val Glu His Gly Phe
645 650 655

Ile Gln Thr Leu Leu Lys Val Thr Leu Glu Val Ile Asp Thr Glu His
660 665 670

Leu Glu Glu Leu Leu His Lys Asp Asp Asp Gly Asp Gly Ser Lys Thr
675 680 685

Lys Glu Met Ser Asn Ser Met Thr Pro Ser Gln Lys Val Trp Tyr Arg
690 695 700

Asp Phe Met Gln Leu Ile Asn His Pro Asn Leu Asn Thr Met Asp Glu
705 710 715 720

Phe Cys Glu Gln Val Trp Lys Arg Asp Arg Lys Gln Arg Arg Gln Arg
725 730 735

Pro Gly His Thr Pro Gly Asn Ser Asn Lys Trp Lys His Leu Gln Glu
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Asn Lys Lys Gly Arg Asn Arg Arg Thr His Glu Phe Glu Arg Ala Pro
755 760 765

Arg Ser Val
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cccgccctcg ccctcactgc tgactcctct tccagatcct ggggcagagt ccagggcagc    180

tcaaggctcc tccacacaca cacccgctga accctgagca ccctgagctg ctgag atg     238
                                                             Met
                                                             1

ggg cgg gcc ggg gct gcc gcc gtg atc ccg ggc ctg gcc ctg ctc tgg      286
Gly Arg Ala Gly Ala Ala Ala Val Ile Pro Gly Leu Ala Leu Leu Trp
            5                   10                  15

gca gtg ggg ctg ggg agt gcc gcc ccc agc ccc cca cgc ctt cgg ctc      334
Ala Val Gly Leu Gly Ser Ala Ala Pro Ser Pro Pro Arg Leu Arg Leu
        20                  25                  30

tcc ttc caa gag ctc cag gcc tgg cat ggt ctc cag act ttc agc ctg      382
Ser Phe Gln Glu Leu Gln Ala Trp His Gly Leu Gln Thr Phe Ser Leu
    35                  40                  45

gag cga acc tgc tgc tac cag gcc ttg ctg gtg gat gag gag cgt gga      430
Glu Arg Thr Cys Cys Tyr Gln Ala Leu Leu Val Asp Glu Glu Arg Gly
50                  55                  60                  65

cgc ctg ttt gtg ggt gcc gag aac cat gtg gcc tcc ctc aac ctg gac      478
Arg Leu Phe Val Gly Ala Glu Asn His Val Ala Ser Leu Asn Leu Asp
                70                  75                  80

aac atc agc aag cgg gcc aag aag ctg gcc tgg ccg gcc cct gtg gaa      526
Asn Ile Ser Lys Arg Ala Lys Lys Leu Ala Trp Pro Ala Pro Val Glu
            85                  90                  95

tgg cga gag gag tgc aac tgg gca ggg aag gac att ggt act gag tgc      574
Trp Arg Glu Glu Cys Asn Trp Ala Gly Lys Asp Ile Gly Thr Glu Cys
        100                 105                 110

atg aac ttc gtg aag ttg ctg cat gcc tac aac cgc acc cat ttg ctg      622
Met Asn Phe Val Lys Leu Leu His Ala Tyr Asn Arg Thr His Leu Leu
    115                 120                 125

gcc tgt ggc acg gga gcc ttc cac cca acc tgt gcc ttt gtg gaa gtg      670
Ala Cys Gly Thr Gly Ala Phe His Pro Thr Cys Ala Phe Val Glu Val
130                 135                 140                 145

ggc cac cgg gca gag gag ccc gtc ctc cgg ctg gac cca gga agg ata      718
Gly His Arg Ala Glu Glu Pro Val Leu Arg Leu Asp Pro Gly Arg Ile
                150                 155                 160

gag gat ggc aag ggg aag agt cct tat gac ccc agg cat cgg gct gcc      766
Glu Asp Gly Lys Gly Lys Ser Pro Tyr Asp Pro Arg His Arg Ala Ala
            165                 170                 175

tcc gtg ctg gtg ggg gag gag cta tac tca ggg gtg gca gca gac ctc      814
Ser Val Leu Val Gly Glu Glu Leu Tyr Ser Gly Val Ala Ala Asp Leu
        180                 185                 190

atg gga cga gac ttt acc atc ttt cgc agc cta ggg caa cgt cca agt      862
Met Gly Arg Asp Phe Thr Ile Phe Arg Ser Leu Gly Gln Arg Pro Ser
    195                 200                 205

ctc cga aca gag cca cac gac tcc cgc tgg ctc aat gag ccc aag ttt      910
Leu Arg Thr Glu Pro His Asp Ser Arg Trp Leu Asn Glu Pro Lys Phe
210                 215                 220                 225
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gtc aag gta ttt tgg atc ccg gag agc gag aac cca gac gac gac aaa      958
Val Lys Val Phe Trp Ile Pro Glu Ser Glu Asn Pro Asp Asp Asp Lys
                230                 235                 240

atc tac ttc ttc ttt cgt gag acg gcg gta gag gcg gcg ccg gca ctg     1006
Ile Tyr Phe Phe Phe Arg Glu Thr Ala Val Glu Ala Ala Pro Ala Leu
            245                 250                 255

gga cgc ctg tcc gtg tcc cgc gtt ggc cag atc tgc cgg aac gac gtg     1054
Gly Arg Leu Ser Val Ser Arg Val Gly Gln Ile Cys Arg Asn Asp Val
        260                 265                 270

ggc ggc cag cgc agc ctg gtc aac aag tgg acg acg ttc ctg aag gcg     1102
Gly Gly Gln Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys Ala
    275                 280                 285

cgg ctg gtg tgc tcg gtg ccc ggc gtc gag ggc gac acc cac ttc gat     1150
Arg Leu Val Cys Ser Val Pro Gly Val Glu Gly Asp Thr His Phe Asp
290                 295                 300                 305

cag ctc cag gat gtg ttt ctg ttg tcc tcg cgg gac cac cgg acc ccg     1198
Gln Leu Gln Asp Val Phe Leu Leu Ser Ser Arg Asp His Arg Thr Pro
                310                 315                 320

ctg ctc tat gcc gtc ttc tcc acg tcc agc agc atc ttc cag ggc tct     1246
Leu Leu Tyr Ala Val Phe Ser Thr Ser Ser Ser Ile Phe Gln Gly Ser
            325                 330                 335

gcg gtg tgc gtg tac agc atg aac gac gtg cgc cgg gcc ttc ttg gga     1294
Ala Val Cys Val Tyr Ser Met Asn Asp Val Arg Arg Ala Phe Leu Gly
        340                 345                 350

ccc ttt gca cac aag gag ggg ccc atg cac cag tgg gtg tca tac cag     1342
Pro Phe Ala His Lys Glu Gly Pro Met His Gln Trp Val Ser Tyr Gln
    355                 360                 365

ggt cgc gtc ccc tac ccg cgg cca ggc atg tgc ccc agc aag acc ttt     1390
Gly Arg Val Pro Tyr Pro Arg Pro Gly Met Cys Pro Ser Lys Thr Phe
370                 375                 380                 385

ggc acc ttc agt tcc acc aag gac ttc cca gac gat gtc atc cag ttt     1438
Gly Thr Phe Ser Ser Thr Lys Asp Phe Pro Asp Asp Val Ile Gln Phe
                390                 395                 400

gcg cgg aac cac ccc ctc atg tac aac tct gtc ctg ccc act ggg ggg     1486
Ala Arg Asn His Pro Leu Met Tyr Asn Ser Val Leu Pro Thr Gly Gly
            405                 410                 415

cgc cct ctt ttc cta caa gtt gga gcc aat tac acc ttc act caa att     1534
Arg Pro Leu Phe Leu Gln Val Gly Ala Asn Tyr Thr Phe Thr Gln Ile
        420                 425                 430


gcc gcg gac cgg gtt gca gcc gct gac gga cac tat gac gtc ctc ttc     1582
Ala Ala Asp Arg Val Ala Ala Ala Asp Gly His Tyr Asp Val Leu Phe
    435                 440                 445

att ggc aca gac gtt ggc acg gtg ctg aag gtg atc tcg gtc ccc aag     1630
Ile Gly Thr Asp Val Gly Thr Val Leu Lys Val Ile Ser Val Pro Lys
450                 455                 460                 465

ggc agt agg ccc agc gca gag ggg ctg ctc ctg gag gag ctg cac gtg     1678
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Gly Ser Arg Pro Ser Ala Glu Gly Leu Leu Leu Glu Glu Leu His Val
                470                 475                 480

ttt gag gac tcg gcc gct gtc acc agc atg caa att tct tcc aag agg      1726
Phe Glu Asp Ser Ala Ala Val Thr Ser Met Gln Ile Ser Ser Lys Arg
            485                 490                 495

cac cag ctg tac gta gcc tcg cgg agc gcg gtg gcc cag atc gcg ttg      1774
His Gln Leu Tyr Val Ala Ser Arg Ser Ala Val Ala Gln Ile Ala Leu
        500                 505                 510

cac cgc tgc gct gcc cac ggc cgc gtc tgc acc gaa tgc tgt ctg gcg      1822
His Arg Cys Ala Ala His Gly Arg Val Cys Thr Glu Cys Cys Leu Ala
    515                 520                 525

cgt gac ccc tac tgc gcc tgg gac ggg gtc gcg tgc acg cgc ttc cag      1870
Arg Asp Pro Tyr Cys Ala Trp Asp Gly Val Ala Cys Thr Arg Phe Gln
530                 535                 540                 545

ccc agt gcc aag agg cgg ttc cgg cgg caa gac gta agg aat ggc gac      1918
Pro Ser Ala Lys Arg Arg Phe Arg Arg Gln Asp Val Arg Asn Gly Asp
                550                 555                 560

ccc agc acg ttg tgc tcc gga gac tcg tct cgt ccc gcg ctg ctg gaa      1966
Pro Ser Thr Leu Cys Ser Gly Asp Ser Ser Arg Pro Ala Leu Leu Glu
            565                 570                 575

cac aag gtg ttc ggc gtg gag ggc agc agc gcc ttt ctg gag tgt gag      2014
His Lys Val Phe Gly Val Glu Gly Ser Ser Ala Phe Leu Glu Cys Glu
        580                 585                 590

ccc cgc tcg ctg cag gcg cgc gtg gag tgg act ttc cag cgc gca ggg      2062
Pro Arg Ser Leu Gln Ala Arg Val Glu Trp Thr Phe Gln Arg Ala Gly
    595                 600                 605

gtg aca gcc cac acc cag gtg ctg gca gag gag cgc acc gag cgc acc      2110
Val Thr Ala His Thr Gln Val Leu Ala Glu Glu Arg Thr Glu Arg Thr
610                 615                 620                 625

gcc cgg gga cta ctg ctg cgc agg ctg cgg cgc cgg gac tcg ggc gtg      2158
Ala Arg Gly Leu Leu Leu Arg Arg Leu Arg Arg Arg Asp Ser Gly Val
                630                 635                 640

tac ttg tgc gcc gcc gtc gag cag ggc ttt acg caa ccg ctg cgt cgc      2206
Tyr Leu Cys Ala Ala Val Glu Gln Gly Phe Thr Gln Pro Leu Arg Arg
            645                 650                 655

ctg tcg ctg cac gtg ttg agt gct acg cag gcc gaa cga ctg gcg cgg      2254
Leu Ser Leu His Val Leu Ser Ala Thr Gln Ala Glu Arg Leu Ala Arg
        660                 665                 670

gcc gag gag gct gcg ccc gcc gcg ccg ccg ggc ccc aaa ctc tgg tac      2302
Ala Glu Glu Ala Ala Pro Ala Ala Pro Pro Gly Pro Lys Leu Trp Tyr
    675                 680                 685


cgg gac ttt ctg cag ctg gtg gag ccg ggc gga ggt ggc agc gcg aac      2350
Arg Asp Phe Leu Gln Leu Val Glu Pro Gly Gly Gly Gly Ser Ala Asn
690                 695                 700                 705

tcc ctg cgc atg tgc cgc ccg cag cct gcg ctg cag tca ctg ccc ctg      2398
Ser Leu Arg Met Cys Arg Pro Gln Pro Ala Leu Gln Ser Leu Pro Leu
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            710                 715                 720

gag tcg cgg aga aag ggc cgt aac cgg agg acc cac gcc cct gag cct      2446
Glu Ser Arg Arg Lys Gly Arg Asn Arg Arg Thr His Ala Pro Glu Pro
            725                 730                 735

cgc gct gag cgg ggg ccg cgc agc gca acg cac tgg tga ccagactgtc      2495
Arg Ala Glu Arg Gly Pro Arg Ser Ala Thr His Trp
        740                 745

cccacgccgg gaaccaagca ggagacgaca ggcgagagag gagccagaca gaccctgaaa    2555

agaaggacgg gttggggccg ggcacattgg gggtcaccgg ccgatggaga caccaaccga    2615

caggccctgg ctgagggcag ctgcgcgggc ttatttatta acaggataac ccttgaatgt    2675

agcagccccg ggagggcggc acaggtcggg cgcaggattc agccggaggg aagggacggg    2735

gaagccgagc tccagagcaa cgaccagggc cgaggaggtg cctggagtgc ccaccctggg    2795

agacagaccc cacctccttg ggtagtgagc agtgagcaga aagctgtgaa caggctgggc    2855

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            20                  25                  30

Leu Ser Phe Gln Glu Leu Gln Ala Trp His Gly Leu Gln Thr Phe Ser
        35                  40                  45

Leu Glu Arg Thr Cys Cys Tyr Gln Ala Leu Leu Val Asp Glu Glu Arg
    50                  55                  60

Gly Arg Leu Phe Val Gly Ala Glu Asn His Val Ala Ser Leu Asn Leu
65                  70                  75                  80

Asp Asn Ile Ser Lys Arg Ala Lys Lys Leu Ala Trp Pro Ala Pro Val
                85                  90                  95
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Glu Trp Arg Glu Glu Cys Asn Trp Ala Gly Lys Asp Ile Gly Thr Glu
100 105 110

Cys Met Asn Phe Val Lys Leu Leu His Ala Tyr Asn Arg Thr His Leu
115 120 125

Leu Ala Cys Gly Thr Gly Ala Phe His Pro Thr Cys Ala Phe Val Glu
130 135 140

Val Gly His Arg Ala Glu Glu Pro Val Leu Arg Leu Asp Pro Gly Arg
145 150 155 160

Ile Glu Asp Gly Lys Gly Lys Ser Pro Tyr Asp Pro Arg His Arg Ala
165 170 175

Ala Ser Val Leu Val Gly Glu Glu Leu Tyr Ser Gly Val Ala Ala Asp
180 185 190

Leu Met Gly Arg Asp Phe Thr Ile Phe Arg Ser Leu Gly Gln Arg Pro
195 200 205

Ser Leu Arg Thr Glu Pro His Asp Ser Arg Trp Leu Asn Glu Pro Lys
210 215 220

Phe Val Lys Val Phe Trp Ile Pro Glu Ser Glu Asn Pro Asp Asp Asp
225 230 235 240

Lys Ile Tyr Phe Phe Phe Arg Glu Thr Ala Val Glu Ala Ala Pro Ala
245 250 255

Leu Gly Arg Leu Ser Val Ser Arg Val Gly Gln Ile Cys Arg Asn Asp
260 265 270

Val Gly Gly Gln Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys
275 280 285

Ala Arg Leu Val Cys Ser Val Pro Gly Val Glu Gly Asp Thr His Phe
290 295 300

Asp Gln Leu Gln Asp Val Phe Leu Leu Ser Ser Arg Asp His Arg Thr
305 310 315 320

Pro Leu Leu Tyr Ala Val Phe Ser Thr Ser Ser Ser Ile Phe Gln Gly
325 330 335

Ser Ala Val Cys Val Tyr Ser Met Asn Asp Val Arg Arg Ala Phe Leu
340 345 350

Gly Pro Phe Ala His Lys Glu Gly Pro Met His Gln Trp Val Ser Tyr
355 360 365

Gln Gly Arg Val Pro Tyr Pro Arg Pro Gly Met Cys Pro Ser Lys Thr
370 375 380

Phe Gly Thr Phe Ser Ser Thr Lys Asp Phe Pro Asp Asp Val Ile Gln
385 390 395 400

Phe Ala Arg Asn His Pro Leu Met Tyr Asn Ser Val Leu Pro Thr Gly
405 410 415

Gly Arg Pro Leu Phe Leu Gln Val Gly Ala Asn Tyr Thr Phe Thr Gln
420 425 430

Ile Ala Ala Asp Arg Val Ala Ala Ala Asp Gly His Tyr Asp Val Leu
435 440 445

Phe Ile Gly Thr Asp Val Gly Thr Val Leu Lys Val Ile Ser Val Pro
450 455 460

Lys Gly Ser Arg Pro Ser Ala Glu Gly Leu Leu Leu Glu Glu Leu His
465 470 475 480

Val Phe Glu Asp Ser Ala Ala Val Thr Ser Met Gln Ile Ser Ser Lys
485 490 495

Arg His Gln Leu Tyr Val Ala Ser Arg Ser Ala Val Ala Gln Ile Ala
500 505 510

Leu His Arg Cys Ala Ala His Gly Arg Val Cys Thr Glu Cys Cys Leu
515 520 525

Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Val Ala Cys Thr Arg Phe
530 535 540

Gln Pro Ser Ala Lys Arg Arg Phe Arg Arg Gln Asp Val Arg Asn Gly
545 550 555 560

Asp Pro Ser Thr Leu Cys Ser Gly Asp Ser Ser Arg Pro Ala Leu Leu
565 570 575

Glu His Lys Val Phe Gly Val Glu Gly Ser Ser Ala Phe Leu Glu Cys
580 585 590

Glu Pro Arg Ser Leu Gln Ala Arg Val Glu Trp Thr Phe Gln Arg Ala
595 600 605

Gly Val Thr Ala His Thr Gln Val Leu Ala Glu Glu Arg Thr Glu Arg
    610   615   620

Thr Ala Arg Gly Leu Leu Leu Arg Arg Leu Arg Arg Arg Asp Ser Gly
625   630   635   640

Val Tyr Leu Cys Ala Ala Val Glu Gln Gly Phe Thr Gln Pro Leu Arg
                645   650   655

Arg Leu Ser Leu His Val Leu Ser Ala Thr Gln Ala Glu Arg Leu Ala
            660   665   670

Arg Ala Glu Glu Ala Ala Pro Ala Ala Pro Pro Gly Pro Lys Leu Trp
        675   680   685

Tyr Arg Asp Phe Leu Gln Leu Val Glu Pro Gly Gly Gly Gly Ser Ala
    690   695   700

Asn Ser Leu Arg Met Cys Arg Pro Gln Pro Ala Leu Gln Ser Leu Pro
705   710   715   720

Leu Glu Ser Arg Arg Lys Gly Arg Asn Arg Arg Thr His Ala Pro Glu
                725   730   735

Pro Arg Ala Glu Arg Gly Pro Arg Ser Ala Thr His Trp
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gctgcgcggt ggtgatgcga gcctgctggg cggcgcgccg gggcagccgg agccgcgcgc   240

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cgcggcgctg taatcggaca ccaagagcgc tcgcccccgg cctccggcca ctttccattc    300

actccgaggt gcttgattga gcgacgcgga gaagagctcc gggtgccgcg gcactgcagc    360

gctgagattc ctttacaaag aaactcagag gaccgggaag aaagaatttc acctttgcga    420

cgtgctagaa aataaggtcg tctgggaaaa ggactggaga cacaagcgca tccaaccccg    480

gtagcaaact gatgactttt ccgtgctgat ttctttcaac ctcggtattt tcccttggat    540

attaacttgc atatctgaag aa atg gca ttc cgg aca att tgc gtg ttg gtt     592
                         Met Ala Phe Arg Thr Ile Cys Val Leu Val
                         1               5                   10

gga gta ttt att tgt tct atc tgt gtg aaa gga tct tcc cag ccc caa      640
Gly Val Phe Ile Cys Ser Ile Cys Val Lys Gly Ser Ser Gln Pro Gln
                15                  20                  25

gca aga gtt tat tta aca ttt gat gaa ctt cga gaa acc aag acc tct      688
Ala Arg Val Tyr Leu Thr Phe Asp Glu Leu Arg Glu Thr Lys Thr Ser
            30                  35                  40

gaa tac ttc agc ctt tcc cac cat cct tta gac tac agg att tta tta      736
Glu Tyr Phe Ser Leu Ser His His Pro Leu Asp Tyr Arg Ile Leu Leu
        45                  50                  55

atg gat gaa gat cag gac cgg ata tat gtg gga agc aaa gat cac att      784
Met Asp Glu Asp Gln Asp Arg Ile Tyr Val Gly Ser Lys Asp His Ile
    60                  65                  70

ctt tcc ctg aat att aac aat ata agt caa gaa gct ttg agt gtt ttc      832
Leu Ser Leu Asn Ile Asn Asn Ile Ser Gln Glu Ala Leu Ser Val Phe
75                  80                  85                  90

tgg cca gca tct aca atc aaa gtt gaa gaa tgc aaa atg gct ggc aaa      880
Trp Pro Ala Ser Thr Ile Lys Val Glu Glu Cys Lys Met Ala Gly Lys
                95                  100                 105

gat ccc aca cac ggc tgt ggg aac ttt gtc cgt gta att cag act ttc      928
Asp Pro Thr His Gly Cys Gly Asn Phe Val Arg Val Ile Gln Thr Phe
            110                 115                 120

aat cgc aca cat ttg tat gtc tgt ggg agt ggc gct ttc agt cct gtc      976
Asn Arg Thr His Leu Tyr Val Cys Gly Ser Gly Ala Phe Ser Pro Val
        125                 130                 135

tgt act tac ttg aac aga ggg agg aga tca gag gac caa gtt ttc atg     1024
Cys Thr Tyr Leu Asn Arg Gly Arg Arg Ser Glu Asp Gln Val Phe Met
    140                 145                 150

att gac tcc aag tgt gaa tct gga aaa gga cgc tgc tct ttc aac ccc     1072
Ile Asp Ser Lys Cys Glu Ser Gly Lys Gly Arg Cys Ser Phe Asn Pro
155                 160                 165                 170

aac gtg aac acg gtg tct gtt atg atc aat gag gag ctt ttc tct gga     1120
Asn Val Asn Thr Val Ser Val Met Ile Asn Glu Glu Leu Phe Ser Gly
                175                 180                 185

atg tat ata gat ttc atg ggg aca gat gct gct att ttt cga agt tta     1168
Met Tyr Ile Asp Phe Met Gly Thr Asp Ala Ala Ile Phe Arg Ser Leu
            190                 195                 200

acc aag agg aat gcg gtc aga act gat caa cat aat tcc aaa tgg cta     1216
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Thr Lys Arg Asn Ala Val Arg Thr Asp Gln His Asn Ser Lys Trp Leu
205 210 215

agt gaa cct atg ttt gta gat gca cat gtc atc cca gat ggt act gat 1264
Ser Glu Pro Met Phe Val Asp Ala His Val Ile Pro Asp Gly Thr Asp
220 225 230

cca aat gat gct aag gtg tac ttc ttc ttc aaa gaa aaa ctg act gac 1312
Pro Asn Asp Ala Lys Val Tyr Phe Phe Phe Lys Glu Lys Leu Thr Asp
235 240 245 250

aat aac agg agc acg aaa cag att cat tcc atg att gct cga ata tgt 1360
Asn Asn Arg Ser Thr Lys Gln Ile His Ser Met Ile Ala Arg Ile Cys
255 260 265

cct aat gac act ggt gga ctg cgt agc ctt gtc aac aag tgg acc act 1408
Pro Asn Asp Thr Gly Gly Leu Arg Ser Leu Val Asn Lys Trp Thr Thr
270 275 280

ttc tta aag gcg agg ctg gtg tgc tcg gta aca gat gaa gac ggc cca 1456
Phe Leu Lys Ala Arg Leu Val Cys Ser Val Thr Asp Glu Asp Gly Pro
285 290 295

gaa aca cac ttt gat gaa tta gag gat gtg ttt ctg ctg gaa act gat 1504
Glu Thr His Phe Asp Glu Leu Glu Asp Val Phe Leu Leu Glu Thr Asp
300 305 310

aac ccg agg aca aca cta gtg tat ggc att ttt aca aca tca agc tca 1552
Asn Pro Arg Thr Thr Leu Val Tyr Gly Ile Phe Thr Thr Ser Ser Ser
315 320 325 330

gtt ttc aaa gga tca gcc gtg tgt gtg tat cat tta tct gat ata cag 1600
Val Phe Lys Gly Ser Ala Val Cys Val Tyr His Leu Ser Asp Ile Gln
335 340 345

act gtg ttt aat ggg cct ttt gcc cac aaa gaa ggg ccc aat cat cag 1648
Thr Val Phe Asn Gly Pro Phe Ala His Lys Glu Gly Pro Asn His Gln
350 355 360

ctg att tcc tat cag ggc aga att cca tat cct cgc cct gga act tgt 1696
Leu Ile Ser Tyr Gln Gly Arg Ile Pro Tyr Pro Arg Pro Gly Thr Cys
365 370 375

cca gga gga gca ttt aca ccc aat atg cga acc acc aag gag ttc cca 1744
Pro Gly Gly Ala Phe Thr Pro Asn Met Arg Thr Thr Lys Glu Phe Pro
380 385 390

gat gat gtt gtc act ttt att cgg aac cat cct ctc atg tac aat tcc 1792
Asp Asp Val Val Thr Phe Ile Arg Asn His Pro Leu Met Tyr Asn Ser
395 400 405 410

atc tac cca atc cac aaa agg cct ttg att gtt cgt att ggc act gac 1840
Ile Tyr Pro Ile His Lys Arg Pro Leu Ile Val Arg Ile Gly Thr Asp
415 420 425

tac aag tac aca aag ata gct gtg gat cga gtg aac gct gct gat ggg 1888
Tyr Lys Tyr Thr Lys Ile Ala Val Asp Arg Val Asn Ala Ala Asp Gly
430 435 440

aga tac cat gtc ctg ttt ctc gga aca gat cgg ggt act gtg caa aaa 1936
Arg Tyr His Val Leu Phe Leu Gly Thr Asp Arg Gly Thr Val Gln Lys
445 450 455

gtg gtt gtt ctt cct act aac aac tct gtc agt ggc gag ctc att ctg 1984
Val Val Val Leu Pro Thr Asn Asn Ser Val Ser Gly Glu Leu Ile Leu
460 465 470

gag gag ctg gaa gtc ttt aag aat cat gct cct ata aca aca atg aaa 2032
Glu Glu Leu Glu Val Phe Lys Asn His Ala Pro Ile Thr Thr Met Lys
475 480 485 490

att tca tct aaa aag caa cag ttg tat gtg agt tcc aat gaa ggg gtt 2080
Ile Ser Ser Lys Lys Gln Gln Leu Tyr Val Ser Ser Asn Glu Gly Val
495 500 505

tcc caa gta tct ctg cac cgc tgc cac atc tat ggt aca gcc tgt gct 2128
Ser Gln Val Ser Leu His Arg Cys His Ile Tyr Gly Thr Ala Cys Ala
510 515 520

gac tgc tgc ctg gcg cgg gac cct tat tgc gcc tgg gat ggc cat tcc 2176
Asp Cys Cys Leu Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly His Ser
525 530 535

tgt tcc aga ttc tac cca act ggg aaa cgg agg agc cga aga caa gat 2224
Cys Ser Arg Phe Tyr Pro Thr Gly Lys Arg Arg Ser Arg Arg Gln Asp
540 545 550

gtg aga cat gga aac cca ctg act caa tgc aga gga ttt aat cta aaa 2272
Val Arg His Gly Asn Pro Leu Thr Gln Cys Arg Gly Phe Asn Leu Lys
555 560 565 570

gca tac aga aat gca gct gaa att gtg cag tat gga gta aaa aat aac 2320
Ala Tyr Arg Asn Ala Ala Glu Ile Val Gln Tyr Gly Val Lys Asn Asn
575 580 585

acc act ttt ctg gag tgt gcc ccc aag tct ccg cag gca tct atc aag 2368
Thr Thr Phe Leu Glu Cys Ala Pro Lys Ser Pro Gln Ala Ser Ile Lys
590 595 600

tgg ctg tta cag aaa gac aaa gac agg agg aaa gag gtt aag ctg aat 2416
Trp Leu Leu Gln Lys Asp Lys Asp Arg Arg Lys Glu Val Lys Leu Asn
605 610 615

gaa cga ata ata gcc act tca cag gga ctc ctg atc cgc tct gtt cag 2464
Glu Arg Ile Ile Ala Thr Ser Gln Gly Leu Leu Ile Arg Ser Val Gln
620 625 630

ggt tct gac caa gga ctt tat cac tgc att gct aca gaa aat agt ttc 2512
Gly Ser Asp Gln Gly Leu Tyr His Cys Ile Ala Thr Glu Asn Ser Phe
635 640 645 650

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Lys Gln Thr Ile Ala Lys Ile Asn Phe Lys Val Leu Asp Ser Glu Met
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gtg gct gtt gtg acg gac aaa tgg tcc ccg tgg acc tgg gcc agc tct 2608
Val Ala Val Val Thr Asp Lys Trp Ser Pro Trp Thr Trp Ala Ser Ser
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gtg agg gct tta ccc ttc cac ccg aag gac atc atg ggg gca ttc agc 2656
Val Arg Ala Leu Pro Phe His Pro Lys Asp Ile Met Gly Ala Phe Ser
685 690 695

cac tca gaa atg cag atg att aac caa tac tgc aaa gac act cgg cag 2704

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His Ser Glu Met Gln Met Ile Asn Gln Tyr Cys Lys Asp Thr Arg Gln
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caa cat cag cag gga gat gaa tca cag aaa atg aga ggg gac tat ggc      2752
Gln His Gln Gln Gly Asp Glu Ser Gln Lys Met Arg Gly Asp Tyr Gly
715                 720                 725                 730

aag tta aag gcc ctc atc aat agt cgg aaa agt aga aac agg agg aat      2800
Lys Leu Lys Ala Leu Ile Asn Ser Arg Lys Ser Arg Asn Arg Arg Asn
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cag ttg cca gag tca taa tattttctta tgtgggtctt atgcttccat              2848
Gln Leu Pro Glu Ser
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35 40 45

His His Pro Leu Asp Tyr Arg Ile Leu Leu Met Asp Glu Asp Gln Asp
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Arg Ile Tyr Val Gly Ser Lys Asp His Ile Leu Ser Leu Asn Ile Asn
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Asn Ile Ser Gln Glu Ala Leu Ser Val Phe Trp Pro Ala Ser Thr Ile
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Lys Val Glu Glu Cys Lys Met Ala Gly Lys Asp Pro Thr His Gly Cys
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Gly Asn Phe Val Arg Val Ile Gln Thr Phe Asn Arg Thr His Leu Tyr
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Val Cys Gly Ser Gly Ala Phe Ser Pro Val Cys Thr Tyr Leu Asn Arg
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Arg Thr Asp Gln His Asn Ser Lys Trp Leu Ser Glu Pro Met Phe Val
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Tyr Phe Phe Phe Lys Glu Lys Leu Thr Asp Asn Asn Arg Ser Thr Lys
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Gln Ile His Ser Met Ile Ala Arg Ile Cys Pro Asn Asp Thr Gly Gly
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Leu Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys Ala Arg Leu
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Val Cys Ser Val Thr Asp Glu Asp Gly Pro Glu Thr His Phe Asp Glu
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Val Tyr Gly Ile Phe Thr Thr Ser Ser Ser Val Phe Lys Gly Ser Ala

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Val Cys Val Tyr His Leu Ser Asp Ile Gln Thr Val Phe Asn Gly Pro
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Pro Asn Met Arg Thr Thr Lys Glu Phe Pro Asp Asp Val Val Thr Phe
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Ile Arg Asn His Pro Leu Met Tyr Asn Ser Ile Tyr Pro Ile His Lys
                405                 410                 415

Arg Pro Leu Ile Val Arg Ile Gly Thr Asp Tyr Lys Tyr Thr Lys Ile
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Ala Val Asp Arg Val Asn Ala Ala Asp Gly Arg Tyr His Val Leu Phe
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Leu Gly Thr Asp Arg Gly Thr Val Gln Lys Val Val Val Leu Pro Thr
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Asn Asn Ser Val Ser Gly Glu Leu Ile Leu Glu Glu Leu Glu Val Phe
465                 470                 475                 480

Lys Asn His Ala Pro Ile Thr Thr Met Lys Ile Ser Ser Lys Lys Gln
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Gln Leu Tyr Val Ser Ser Asn Glu Gly Val Ser Gln Val Ser Leu His
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Arg Cys His Ile Tyr Gly Thr Ala Cys Ala Asp Cys Cys Leu Ala Arg
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Asp Pro Tyr Cys Ala Trp Asp Gly His Ser Cys Ser Arg Phe Tyr Pro
    530                 535                 540

Thr Gly Lys Arg Arg Ser Arg Arg Gln Asp Val Arg His Gly Asn Pro
545                 550                 555                 560

Leu Thr Gln Cys Arg Gly Phe Asn Leu Lys Ala Tyr Arg Asn Ala Ala
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Ala Pro Lys Ser Pro Gln Ala Ser Ile Lys Trp Leu Leu Gln Lys Asp
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Lys Asp Arg Arg Lys Glu Val Lys Leu Asn Glu Arg Ile Ile Ala Thr
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Ser Gln Gly Leu Leu Ile Arg Ser Val Gln Gly Ser Asp Gln Gly Leu
625                 630                 635                 640

Tyr His Cys Ile Ala Thr Glu Asn Ser Phe Lys Gln Thr Ile Ala Lys
                645                 650                 655

Ile Asn Phe Lys Val Leu Asp Ser Glu Met Val Ala Val Val Thr Asp
            660                 665                 670

Lys Trp Ser Pro Trp Thr Trp Ala Ser Ser Val Arg Ala Leu Pro Phe
        675                 680                 685

His Pro Lys Asp Ile Met Gly Ala Phe Ser His Ser Glu Met Gln Met
    690                 695                 700

Ile Asn Gln Tyr Cys Lys Asp Thr Arg Gln Gln His Gln Gln Gly Asp
705                 710                 715                 720

Glu Ser Gln Lys Met Arg Gly Asp Tyr Gly Lys Leu Lys Ala Leu Ile
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tttttctga atgaacagct ttgcccaagt gactgaaaaa tacagcttct tcctgaatct     180

accggcgtag ttgctgaaga gcgctctaga caggacatgg ctctgaagac tcactctttg     240

gaatgtcctc ttgctcccgg cttataaaca actgtcccga ggaaagaaag gttttacata     300

gccaaataca gcctgacaaa tggcacttcg gaactgtgct ttctgatgac aacgcgttcg     360

atttctgaca aagcctctcg cacgctgccc ctggagggaa gtcctaagta aaactcagac     420

cctccttaaa gtgaggagcg agggcttgga cggtgaacac ggcagc atg gca tcc        475
                                                   Met Ala Ser
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gcg ggg cac att atc acc ttg ctc ctg tgg ggt tac tta ctg gag ctt      523
Ala Gly His Ile Ile Thr Leu Leu Leu Trp Gly Tyr Leu Leu Glu Leu
    5                   10                  15

tgg aca gga ggt cat aca gct gat act acc cac ccc cgg tta cgc ctg      571
Trp Thr Gly Gly His Thr Ala Asp Thr Thr His Pro Arg Leu Arg Leu
20                  25                  30                  35

tca cat aaa gag ctc ttg aat ctg aac aga aca tca ata ttt cat agc      619
Ser His Lys Glu Leu Leu Asn Leu Asn Arg Thr Ser Ile Phe His Ser
                40                  45                  50

cct ttt gga ttt ctt gat ctc cat aca atg ctg ctg gat gaa tat caa      667
Pro Phe Gly Phe Leu Asp Leu His Thr Met Leu Leu Asp Glu Tyr Gln
            55                  60                  65

gag agg ctc ttc gtg gga ggc agg gac ctt gta tat tcc ctc agc ttg      715
Glu Arg Leu Phe Val Gly Gly Arg Asp Leu Val Tyr Ser Leu Ser Leu
        70                  75                  80

gag aga atc agt gac ggc tat aaa gag ata cac tgg ccg agt aca gct      763
Glu Arg Ile Ser Asp Gly Tyr Lys Glu Ile His Trp Pro Ser Thr Ala
    85                  90                  95

cta aaa atg gaa gaa tgc ata atg aag gga aaa gat gcg ggt gaa tgt      811
Leu Lys Met Glu Glu Cys Ile Met Lys Gly Lys Asp Ala Gly Glu Cys
100                 105                 110                 115

gca aat tat gtt cgg gtt ttg cat cac tat aac agg aca cac ctt ctg      859
Ala Asn Tyr Val Arg Val Leu His His Tyr Asn Arg Thr His Leu Leu
                120                 125                 130

acc tgt ggt act gga gct ttt gat cca gtt tgt gcc ttc atc aga gtt      907
Thr Cys Gly Thr Gly Ala Phe Asp Pro Val Cys Ala Phe Ile Arg Val
            135                 140                 145

gga tat cat ttg gag gat cct ctg ttt cac ctg gaa tca ccc aga tct      955
Gly Tyr His Leu Glu Asp Pro Leu Phe His Leu Glu Ser Pro Arg Ser
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gag aga gga agg ggc aga tgt cct ttt gac ccc agc tcc tcc ttc atc     1003
Glu Arg Gly Arg Gly Arg Cys Pro Phe Asp Pro Ser Ser Ser Phe Ile
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tcc act tta att ggt agt gaa ttg ttt gct gga ctc tac agt gac tac      1051
Ser Thr Leu Ile Gly Ser Glu Leu Phe Ala Gly Leu Tyr Ser Asp Tyr
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tgg agc aga gac gct gcg atc ttc cgc agc atg ggg cga ctg gcc cat      1099
Trp Ser Arg Asp Ala Ala Ile Phe Arg Ser Met Gly Arg Leu Ala His
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atc cgc act gag cat gac gat gag cgt ctg ttg aaa gaa cca aaa ttt      1147
Ile Arg Thr Glu His Asp Asp Glu Arg Leu Leu Lys Glu Pro Lys Phe
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gta ggt tca tac atg att cct gac aat gaa gac aga gat gac aac aaa      1195
Val Gly Ser Tyr Met Ile Pro Asp Asn Glu Asp Arg Asp Asp Asn Lys
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gta tat ttc ttt ttt act gag aag gca ctg gag gca gaa aac aat gct      1243
Val Tyr Phe Phe Phe Thr Glu Lys Ala Leu Glu Ala Glu Asn Asn Ala
    245                 250                 255

cac gca att tac acc agg gtc ggg cga ctc tgt gtg aat gat gta gga      1291
His Ala Ile Tyr Thr Arg Val Gly Arg Leu Cys Val Asn Asp Val Gly
260                 265                 270                 275

ggg cag aga ata ctg gtg aat aag tgg agc act ttc cta aaa gcg aga      1339
Gly Gln Arg Ile Leu Val Asn Lys Trp Ser Thr Phe Leu Lys Ala Arg
                280                 285                 290


ctc gtt tgc tca gta cca gga atg aat gga att gac aca tat ttt gat      1387
Leu Val Cys Ser Val Pro Gly Met Asn Gly Ile Asp Thr Tyr Phe Asp
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gaa tta gag gac gtt ttt ttg cta cct acc aga gat cat aag aat cca      1435
Glu Leu Glu Asp Val Phe Leu Leu Pro Thr Arg Asp His Lys Asn Pro
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gtg ata ttt gga ctc ttt aac act acc agt aat att ttt cga ggg cat      1483
Val Ile Phe Gly Leu Phe Asn Thr Thr Ser Asn Ile Phe Arg Gly His
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gct ata tgt gtc tat cac atg tct agc att cgg gca gcc ttc aac gga      1531
Ala Ile Cys Val Tyr His Met Ser Ser Ile Arg Ala Ala Phe Asn Gly
340                 345                 350                 355

cca tat gca cat aag gaa gga cct gaa tac cac tgg tca gtc tat gaa      1579
Pro Tyr Ala His Lys Glu Gly Pro Glu Tyr His Trp Ser Val Tyr Glu
                360                 365                 370

gga aaa gtc cct tat cca agg cct ggt tct tgt gcc agc aaa gta aat      1627
Gly Lys Val Pro Tyr Pro Arg Pro Gly Ser Cys Ala Ser Lys Val Asn
            375                 380                 385

gga ggg aga tac gga acc acc aag gac tat cct gat gat gcc atc cga      1675
Gly Gly Arg Tyr Gly Thr Thr Lys Asp Tyr Pro Asp Asp Ala Ile Arg
        390                 395                 400

ttt gca aga agt cat cca cta atg tac cag gcc ata aaa cct gcc cat      1723
Phe Ala Arg Ser His Pro Leu Met Tyr Gln Ala Ile Lys Pro Ala His
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aaa aaa cca ata ttg gta aaa aca gat gga aaa tat aac ctg aaa caa      1771
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Lys Lys Pro Ile Leu Val Lys Thr Asp Gly Lys Tyr Asn Leu Lys Gln
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Ile Ala Val Asp Arg Val Glu Ala Glu Asp Gly Gln Tyr Asp Val Leu
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Phe Ile Gly Thr Asp Asn Gly Ile Val Leu Lys Val Ile Thr Ile Tyr
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aac caa gaa atg gaa tca atg gaa gaa gta att cta gaa gaa ctt cag      1915
Asn Gln Glu Met Glu Ser Met Glu Glu Val Ile Leu Glu Glu Leu Gln
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Ile Phe Lys Asp Pro Val Pro Ile Ile Ser Met Glu Ile Ser Ser Lys
    485                 490                 495

cgg caa cag ctg tat att gga tct gct tct gct gtg gct caa gtc aga      2011
Arg Gln Gln Leu Tyr Ile Gly Ser Ala Ser Ala Val Ala Gln Val Arg
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ttc cat cac tgt gac atg tat gga agt gct tgt gct gac tgc tgc ctg      2059
Phe His His Cys Asp Met Tyr Gly Ser Ala Cys Ala Asp Cys Cys Leu
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gct cga gac cct tac tgt gcc tgg gat ggc ata tcc tgc tcc cgg tat      2107
Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Ile Ser Cys Ser Arg Tyr
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tac cca aca ggc aca cat gca aaa agg cgt ttc cgg aga caa gat gtt      2155
Tyr Pro Thr Gly Thr His Ala Lys Arg Arg Phe Arg Arg Gln Asp Val
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cga cat gga aat gca gct cag cag tgc ttt gga caa cag ttt gtt ggg      2203
Arg His Gly Asn Ala Ala Gln Gln Cys Phe Gly Gln Gln Phe Val Gly
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gat gct ttg gat aag act gaa gaa cat ctg gct tat ggc ata gag aac      2251
Asp Ala Leu Asp Lys Thr Glu Glu His Leu Ala Tyr Gly Ile Glu Asn
580                 585                 590                 595

aac agt act ttg ctg gaa tgt acc cca cga tct tta caa gcg aaa gtt      2299
Asn Ser Thr Leu Leu Glu Cys Thr Pro Arg Ser Leu Gln Ala Lys Val
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atc tgg ttt gta cag aaa gga cgt gag aca aga aaa gag gag gtg aag      2347
Ile Trp Phe Val Gln Lys Gly Arg Glu Thr Arg Lys Glu Glu Val Lys
            615                 620                 625

aca gat gac aga gtg gtt aag atg gac ctt ggt tta ctc ttc cta agg      2395
Thr Asp Asp Arg Val Val Lys Met Asp Leu Gly Leu Leu Phe Leu Arg
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Leu His Lys Ser Asp Ala Gly Thr Tyr Phe Cys Gln Thr Val Glu His
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agc ttt gtc cat acg gtc cgt aaa atc acc ttg gag gta gtg gaa gag      2491
Ser Phe Val His Thr Val Arg Lys Ile Thr Leu Glu Val Val Glu Glu
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cac agg atg cct tgt cct gct cag agt agc atc tcg cag gga gca aaa      2587
His Arg Met Pro Cys Pro Ala Gln Ser Ser Ile Ser Gln Gly Ala Lys
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Pro Trp Tyr Lys Glu Phe Leu Gln Leu Ile Gly Tyr Ser Asn Phe Gln
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aga gtg gaa gaa tac tgc gag aaa gta tgg tgc aca gat aga aag agg      2683
Arg Val Glu Glu Tyr Cys Glu Lys Val Trp Cys Thr Asp Arg Lys Arg
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aaa aag ctt aaa atg tca ccc tcc aag tgg aag tat gcc aac cct cag      2731
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gaa aag aag ctc cgt tcc aaa cct gag cat tac cgc ctg ccc agg cac      2779
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ttaacaaaaa agattttact tcgtgattcc acgtctataa ttctatattg ctaatttttt 5834

cttttgtgtg aattactgaa tatttcagag caaagctatc aacttggaga aacagggatt 5894

aaaaataagg ataaacacta ataagagctc tagaaaaaag ggaacagaaa gtctgcctgt 5954

ttagtaagtg gcaattccat acatatttta gagttttttc tatctaaaat tagttaaata 6014

cttagaatgt ttgtaatgag tgttcgatat ttgctatagg ttttagggtt ttgtaaatct 6074

tcatagtaat tataaacatt tgtaaaattt gtaaaatact ataagtcatt ttgagtgttg 6134

gtgttaagca tgaaacaaac agcagctgtt gtccttaaaa atgaattgac ctggccgggc 6194

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<210> 16

<211> 775

<212> PRT

<213> Homo sapiens

<400> 16

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Leu Glu Leu Trp Thr Gly Gly His Thr Ala Asp Thr Thr His Pro Arg
20 25 30

Leu Arg Leu Ser His Lys Glu Leu Leu Asn Leu Asn Arg Thr Ser Ile
35 40 45

Phe His Ser Pro Phe Gly Phe Leu Asp Leu His Thr Met Leu Leu Asp
50 55 60

Glu Tyr Gln Glu Arg Leu Phe Val Gly Gly Arg Asp Leu Val Tyr Ser
65 70 75 80

Leu Ser Leu Glu Arg Ile Ser Asp Gly Tyr Lys Glu Ile His Trp Pro
85 90 95

Ser Thr Ala Leu Lys Met Glu Glu Cys Ile Met Lys Gly Lys Asp Ala
100 105 110

Gly Glu Cys Ala Asn Tyr Val Arg Val Leu His His Tyr Asn Arg Thr
115 120 125

His Leu Leu Thr Cys Gly Thr Gly Ala Phe Asp Pro Val Cys Ala Phe
130 135 140

Ile Arg Val Gly Tyr His Leu Glu Asp Pro Leu Phe His Leu Glu Ser
145 150 155 160

Pro Arg Ser Glu Arg Gly Arg Gly Arg Cys Pro Phe Asp Pro Ser Ser
165 170 175

Ser Phe Ile Ser Thr Leu Ile Gly Ser Glu Leu Phe Ala Gly Leu Tyr
180 185 190

Ser Asp Tyr Trp Ser Arg Asp Ala Ala Ile Phe Arg Ser Met Gly Arg
195 200 205

Leu Ala His Ile Arg Thr Glu His Asp Asp Glu Arg Leu Leu Lys Glu
210 215 220

Pro Lys Phe Val Gly Ser Tyr Met Ile Pro Asp Asn Glu Asp Arg Asp
225 230 235 240

Asp Asn Lys Val Tyr Phe Phe Phe Thr Glu Lys Ala Leu Glu Ala Glu
245 250 255

Asn Asn Ala His Ala Ile Tyr Thr Arg Val Gly Arg Leu Cys Val Asn
260 265 270

Asp Val Gly Gly Gln Arg Ile Leu Val Asn Lys Trp Ser Thr Phe Leu
275 280 285

Lys Ala Arg Leu Val Cys Ser Val Pro Gly Met Asn Gly Ile Asp Thr
290 295 300

Tyr Phe Asp Glu Leu Glu Asp Val Phe Leu Leu Pro Thr Arg Asp His
305 310 315 320

Lys Asn Pro Val Ile Phe Gly Leu Phe Asn Thr Thr Ser Asn Ile Phe
325 330 335

Arg Gly His Ala Ile Cys Val Tyr His Met Ser Ser Ile Arg Ala Ala
340 345 350

Phe Asn Gly Pro Tyr Ala His Lys Glu Gly Pro Glu Tyr His Trp Ser
355 360 365

Val Tyr Glu Gly Lys Val Pro Tyr Pro Arg Pro Gly Ser Cys Ala Ser
370 375 380

Lys Val Asn Gly Gly Arg Tyr Gly Thr Thr Lys Asp Tyr Pro Asp Asp
385 390 395 400

Ala Ile Arg Phe Ala Arg Ser His Pro Leu Met Tyr Gln Ala Ile Lys
405 410 415

Pro Ala His Lys Lys Pro Ile Leu Val Lys Thr Asp Gly Lys Tyr Asn
420 425 430

Leu Lys Gln Ile Ala Val Asp Arg Val Glu Ala Glu Asp Gly Gln Tyr
435 440 445

Asp Val Leu Phe Ile Gly Thr Asp Asn Gly Ile Val Leu Lys Val Ile
450 455 460

Thr Ile Tyr Asn Gln Glu Met Glu Ser Met Glu Glu Val Ile Leu Glu
465 470 475 480

Glu Leu Gln Ile Phe Lys Asp Pro Val Pro Ile Ile Ser Met Glu Ile
485 490 495

Ser Ser Lys Arg Gln Gln Leu Tyr Ile Gly Ser Ala Ser Ala Val Ala
500 505 510

Gln Val Arg Phe His His Cys Asp Met Tyr Gly Ser Ala Cys Ala Asp
515 520 525

Cys Cys Leu Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Ile Ser Cys
530 535 540

Ser Arg Tyr Tyr Pro Thr Gly Thr His Ala Lys Arg Arg Phe Arg Arg
545 550 555 560

Gln Asp Val Arg His Gly Asn Ala Ala Gln Gln Cys Phe Gly Gln Gln
565 570 575

Phe Val Gly Asp Ala Leu Asp Lys Thr Glu Glu His Leu Ala Tyr Gly
580 585 590

Ile Glu Asn Asn Ser Thr Leu Leu Glu Cys Thr Pro Arg Ser Leu Gln
595 600 605

Ala Lys Val Ile Trp Phe Val Gln Lys Gly Arg Glu Thr Arg Lys Glu

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    610                 615                 620

Glu Val Lys Thr Asp Asp Arg Val Val Lys Met Asp Leu Gly Leu Leu
625                 630                 635                 640

Phe Leu Arg Leu His Lys Ser Asp Ala Gly Thr Tyr Phe Cys Gln Thr
                645                 650                 655

Val Glu His Ser Phe Val His Thr Val Arg Lys Ile Thr Leu Glu Val
            660                 665                 670

Val Glu Glu Glu Lys Val Glu Asp Met Phe Asn Lys Asp Asp Glu Glu
        675                 680                 685

Asp Arg His His Arg Met Pro Cys Pro Ala Gln Ser Ser Ile Ser Gln
    690                 695                 700

Gly Ala Lys Pro Trp Tyr Lys Glu Phe Leu Gln Leu Ile Gly Tyr Ser
705                 710                 715                 720

Asn Phe Gln Arg Val Glu Glu Tyr Cys Glu Lys Val Trp Cys Thr Asp
                725                 730                 735

Arg Lys Arg Lys Lys Leu Lys Met Ser Pro Ser Lys Trp Lys Tyr Ala
            740                 745                 750

Asn Pro Gln Glu Lys Lys Leu Arg Ser Lys Pro Glu His Tyr Arg Leu
        755                 760                 765

Pro Arg His Thr Leu Asp Ser
    770                 775
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<210> 17

<211> 2719

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (79)..(2436)

<400> 17

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ccctaggccc ctcccaca atg ctt gtc gcc ggt ctt ctt ctc tgg gct tcc      111
                    Met Leu Val Ala Gly Leu Leu Leu Trp Ala Ser
                    1               5                   10

cta ctg acc ggg gcc tgg cca tcc ttc ccc acc cag gac cac ctc ccg      159
Leu Leu Thr Gly Ala Trp Pro Ser Phe Pro Thr Gln Asp His Leu Pro
            15                  20                  25

gcc acg ccc cgg gtc cgg ctc tca ttc aaa gag ctg aag gcc aca ggc      207
Ala Thr Pro Arg Val Arg Leu Ser Phe Lys Glu Leu Lys Ala Thr Gly
        30                  35                  40

acc gcc cac ttc ttc aac ttc ctg ctc aac aca acc gac tac cga atc      255
Thr Ala His Phe Phe Asn Phe Leu Leu Asn Thr Thr Asp Tyr Arg Ile
    45                  50                  55

ttg ctc aag gac gag gac cac gac cgc atg tac gtg ggc agc aag gac      303
Leu Leu Lys Asp Glu Asp His Asp Arg Met Tyr Val Gly Ser Lys Asp
60                  65                  70                  75

tac gtg ctg tcc ctg gac ctg cac gac atc aac cgc gag ccc ctc att      351
Tyr Val Leu Ser Leu Asp Leu His Asp Ile Asn Arg Glu Pro Leu Ile
                80                  85                  90

ata cac tgg gca gcc tcc cca cag cgc atc gag gaa tgc gtg ctc tca      399
Ile His Trp Ala Ala Ser Pro Gln Arg Ile Glu Glu Cys Val Leu Ser
            95                  100                 105

ggc aag gat gtc aac ggc gag tgt ggg aac ttc gtc agg ctc atc cag      447
Gly Lys Asp Val Asn Gly Glu Cys Gly Asn Phe Val Arg Leu Ile Gln
        110                 115                 120

ccc tgg aac cga aca cac ctg tat gtg tgc ggg aca ggt gcc tac aac      495
Pro Trp Asn Arg Thr His Leu Tyr Val Cys Gly Thr Gly Ala Tyr Asn
    125                 130                 135

ccc atg tgc acc tat gtg aac cgc gga cgc cgc gcc cag gcc aca cca      543
Pro Met Cys Thr Tyr Val Asn Arg Gly Arg Arg Ala Gln Ala Thr Pro
140                 145                 150                 155

tgg acc cag act cag gcg gtc aga ggc cgc ggc agc aga gcc acg gat      591
Trp Thr Gln Thr Gln Ala Val Arg Gly Arg Gly Ser Arg Ala Thr Asp
                160                 165                 170

ggt gcc ctc cgc ccg atg ccc aca gcc cca cgc cag gat tac atc ttc      639
Gly Ala Leu Arg Pro Met Pro Thr Ala Pro Arg Gln Asp Tyr Ile Phe
            175                 180                 185

tac ctg gag cct gag cga ctc gag tca ggg aag ggc aag tgt ccg tac      687
Tyr Leu Glu Pro Glu Arg Leu Glu Ser Gly Lys Gly Lys Cys Pro Tyr
        190                 195                 200

gat ccc aag ctg gac aca gca tcg gcc ctc atc aat gag gag ctc tat      735
Asp Pro Lys Leu Asp Thr Ala Ser Ala Leu Ile Asn Glu Glu Leu Tyr
    205                 210                 215

gct ggt gtg tac atc gat ttt atg ggc act gat gca gcc atc ttc cgc      783
Ala Gly Val Tyr Ile Asp Phe Met Gly Thr Asp Ala Ala Ile Phe Arg
220                 225                 230                 235

aca ctt gga aag cag aca gcc atg cgc acg gat cag tac aac tcc cgg      831
Thr Leu Gly Lys Gln Thr Ala Met Arg Thr Asp Gln Tyr Asn Ser Arg
                240                 245                 250
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tgg ctg aac gac ccg tcg ttc atc cat gct gag ctc att cct gac agt      879
Trp Leu Asn Asp Pro Ser Phe Ile His Ala Glu Leu Ile Pro Asp Ser
            255                 260                 265

gcg gag cgc aat gat gat aag ctt tac ttc ttc ttc cgt gag cgg tcg      927
Ala Glu Arg Asn Asp Asp Lys Leu Tyr Phe Phe Phe Arg Glu Arg Ser
        270                 275                 280

gca gag gcg ccg cag agc ccc gcg gtg tac gcc cgc atc ggg cgc att      975
Ala Glu Ala Pro Gln Ser Pro Ala Val Tyr Ala Arg Ile Gly Arg Ile
    285                 290                 295

tgc ctg aac gat gac ggt ggt cac tgt tgc ctg gtc aac aag tgg agc     1023
Cys Leu Asn Asp Asp Gly Gly His Cys Cys Leu Val Asn Lys Trp Ser
300                 305                 310                     315

aca ttc ctg aag gcg cgg ctc gtc tgc tct gtc ccg ggc gag gat ggc     1071
Thr Phe Leu Lys Ala Arg Leu Val Cys Ser Val Pro Gly Glu Asp Gly
                320                 325                 330

att gag act cac ttt gat gag ctc cag gac gtg ttt gtc cag cag acc     1119
Ile Glu Thr His Phe Asp Glu Leu Gln Asp Val Phe Val Gln Gln Thr
            335                 340                 345

cag gac gtg agg aac cct gtc att tac gct gtc ttt acc tcc tct ggc     1167
Gln Asp Val Arg Asn Pro Val Ile Tyr Ala Val Phe Thr Ser Ser Gly
        350                 355                 360

tcc gtg ttc cga ggc tct gcc gtg tgt gtc tac tcc atg gct gat att     1215
Ser Val Phe Arg Gly Ser Ala Val Cys Val Tyr Ser Met Ala Asp Ile
    365                 370                 375

cgc atg gtc ttc aac ggg ccc ttt gcc cac aaa gag ggg ccc aac tac     1263
Arg Met Val Phe Asn Gly Pro Phe Ala His Lys Glu Gly Pro Asn Tyr
380                 385                 390                     395

cag tgg atg ccc ttc tca ggg aag atg ccc tac cca cgg ccg ggc acg     1311
Gln Trp Met Pro Phe Ser Gly Lys Met Pro Tyr Pro Arg Pro Gly Thr
                400                 405                 410

tgc cct ggt gga acc ttc acg cca tct atg aag tcc acc aag gat tat     1359
Cys Pro Gly Gly Thr Phe Thr Pro Ser Met Lys Ser Thr Lys Asp Tyr
            415                 420                 425

cct gat gag gtg atc aac ttc atg cgc agc cac cca ctc atg tac cag     1407
Pro Asp Glu Val Ile Asn Phe Met Arg Ser His Pro Leu Met Tyr Gln
        430                 435                 440

gcc gtg tac cct ctg cag cgg cgg ccc ctg gta gtc cgc aca ggt gct     1455
Ala Val Tyr Pro Leu Gln Arg Arg Pro Leu Val Val Arg Thr Gly Ala
    445                 450                 455


ccc tac cgc ctt acc act att gcc gtg gac cag gtg gat gca ggc gac     1503
Pro Tyr Arg Leu Thr Thr Ile Ala Val Asp Gln Val Asp Ala Gly Asp
460                 465                 470                     475

ggg cgc tat gag gtg ctt ttc ctg ggc aca gac cgc ggg aca gtg cag     1551
Gly Arg Tyr Glu Val Leu Phe Leu Gly Thr Asp Arg Gly Thr Val Gln
                480                 485                 490

aag gtc att gtg ctg ccc aag gat gac cag gag atg gag gag ctc atg     1599
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Lys Val Ile Val Leu Pro Lys Asp Asp Gln Glu Met Glu Glu Leu Met
            495                 500                 505

ctg gag gag gtg gag gtc ttc aag gat cca gca ccc gtc aag acc atg      1647
Leu Glu Glu Val Glu Val Phe Lys Asp Pro Ala Pro Val Lys Thr Met
        510                 515                 520

acc atc tct tct aag agg caa caa ctc tac gtg gcg tca gcc gtg ggt      1695
Thr Ile Ser Ser Lys Arg Gln Gln Leu Tyr Val Ala Ser Ala Val Gly
    525                 530                 535

gtc aca cac ctg agc ctg cac cgc tgc cag gcg tat ggg gct gcc tgt      1743
Val Thr His Leu Ser Leu His Arg Cys Gln Ala Tyr Gly Ala Ala Cys
540                 545                 550                 555

gct gac tgc tgc ctt gcc cgg gac cct tac tgt gcc tgg gat ggc cag      1791
Ala Asp Cys Cys Leu Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Gln
                560                 565                 570

gcc tgc tcc cgc tat aca gca tcc tcc aag agg cgg agc cgc cgg cag      1839
Ala Cys Ser Arg Tyr Thr Ala Ser Ser Lys Arg Arg Ser Arg Arg Gln
            575                 580                 585

gac gtc cgg cac gga aac ccc atc agg cag tgc cgt ggg ttc aac tcc      1887
Asp Val Arg His Gly Asn Pro Ile Arg Gln Cys Arg Gly Phe Asn Ser
        590                 595                 600

aat gcc aac aag aat gcc gtg gag tct gtg cag tat ggc gtg gcc ggc      1935
Asn Ala Asn Lys Asn Ala Val Glu Ser Val Gln Tyr Gly Val Ala Gly
    605                 610                 615

agc gca gcc ttc ctt gag tgc cag ccc cgc tcg ccc caa gcc act gtt      1983
Ser Ala Ala Phe Leu Glu Cys Gln Pro Arg Ser Pro Gln Ala Thr Val
620                 625                 630                 635

aag tgg ctg ttc cag cga gat cct ggt gac cgg cgc cga gag att cgt      2031
Lys Trp Leu Phe Gln Arg Asp Pro Gly Asp Arg Arg Arg Glu Ile Arg
                640                 645                 650

gca gag gac cgc ttc ctg cgc aca gag cag ggc ttg ttg ctc cgt gca      2079
Ala Glu Asp Arg Phe Leu Arg Thr Glu Gln Gly Leu Leu Leu Arg Ala
            655                 660                 665

ctg cag ctc agc gat cgt ggc ctc tac tcc tgc aca gcc act gag aac      2127
Leu Gln Leu Ser Asp Arg Gly Leu Tyr Ser Cys Thr Ala Thr Glu Asn
        670                 675                 680

aac ttt aag cac gtc gtc aca cga gtg cag ctg cat gta ctg ggc cgg      2175
Asn Phe Lys His Val Val Thr Arg Val Gln Leu His Val Leu Gly Arg
    685                 690                 695

gac gcc gtc cat gct gcc ctc ttc cca cca ctg tcc atg agc gcc ccg      2223
Asp Ala Val His Ala Ala Leu Phe Pro Pro Leu Ser Met Ser Ala Pro
700                 705                 710                 715

cca ccc cca ggc gca ggc ccc cca acg cct cct tac cag gag tta gcc      2271
Pro Pro Pro Gly Ala Gly Pro Pro Thr Pro Pro Tyr Gln Glu Leu Ala
                720                 725                 730

cag ctg ctg gcc cag cca gaa gtg ggc ctc atc cac cag tac tgc cag      2319
Gln Leu Leu Ala Gln Pro Glu Val Gly Leu Ile His Gln Tyr Cys Gln
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            735                     740                     745

ggt tac tgg cgc cat gtg ccc ccc agc ccc agg gag gct cca ggg gca      2367
Gly Tyr Trp Arg His Val Pro Pro Ser Pro Arg Glu Ala Pro Gly Ala
        750                     755                     760

ccc cgg tct cct gag ccc cag gac cag aaa aag ccc cgg aac cgc cgg      2415
Pro Arg Ser Pro Glu Pro Gln Asp Gln Lys Lys Pro Arg Asn Arg Arg
    765                     770                     775

cac cac cct ccg gac aca tga ggccagctgc ctgtgcctgc catgggccag         2466
His His Pro Pro Asp Thr
780                     785

gctaggcctt ggtccctttt aatataaaag atatatatat atatatatat atatattaaa   2526

atatcggggt gggggtgat tggaagggag ggaggtggcc ttcccaatgc gcgttattcg    2586

gggttattga agaataatat tgcaagtgac agccagaagt agactttctg tcctcacacc   2646

gaagaacccg agtgagcagg agggagggag agacgcgaag agaccttttt tcctttttgg   2706

agaccttgtc cgc                                                       2719
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<210> 18

<211> 785

<212> PRT

<213> Homo sapiens

<400> 18

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Met Leu Val Ala Gly Leu Leu Leu Trp Ala Ser Leu Leu Thr Gly Ala
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Trp Pro Ser Phe Pro Thr Gln Asp His Leu Pro Ala Thr Pro Arg Val
            20                  25                  30

Arg Leu Ser Phe Lys Glu Leu Lys Ala Thr Gly Thr Ala His Phe Phe
        35                  40                  45

Asn Phe Leu Leu Asn Thr Thr Asp Tyr Arg Ile Leu Leu Lys Asp Glu
    50                  55                  60

Asp His Asp Arg Met Tyr Val Gly Ser Lys Asp Tyr Val Leu Ser Leu
65                  70                  75                  80

Asp Leu His Asp Ile Asn Arg Glu Pro Leu Ile Ile His Trp Ala Ala
                85                  90                  95

Ser Pro Gln Arg Ile Glu Glu Cys Val Leu Ser Gly Lys Asp Val Asn
            100                 105                 110
```

```
Gly Glu Cys Gly Asn Phe Val Arg Leu Ile Gln Pro Trp Asn Arg Thr
        115                 120                 125

His Leu Tyr Val Cys Gly Thr Gly Ala Tyr Asn Pro Met Cys Thr Tyr
    130                 135                 140

Val Asn Arg Gly Arg Arg Ala Gln Ala Thr Pro Trp Thr Gln Thr Gln
145                 150                 155                 160

Ala Val Arg Gly Arg Gly Ser Arg Ala Thr Asp Gly Ala Leu Arg Pro
                165                 170                 175

Met Pro Thr Ala Pro Arg Gln Asp Tyr Ile Phe Tyr Leu Glu Pro Glu
            180                 185                 190

Arg Leu Glu Ser Gly Lys Gly Lys Cys Pro Tyr Asp Pro Lys Leu Asp
        195                 200                 205

Thr Ala Ser Ala Leu Ile Asn Glu Glu Leu Tyr Ala Gly Val Tyr Ile
    210                 215                 220

Asp Phe Met Gly Thr Asp Ala Ala Ile Phe Arg Thr Leu Gly Lys Gln
225                 230                 235                 240

Thr Ala Met Arg Thr Asp Gln Tyr Asn Ser Arg Trp Leu Asn Asp Pro
                245                 250                 255

Ser Phe Ile His Ala Glu Leu Ile Pro Asp Ser Ala Glu Arg Asn Asp
            260                 265                 270

Asp Lys Leu Tyr Phe Phe Phe Arg Glu Arg Ser Ala Glu Ala Pro Gln
        275                 280                 285

Ser Pro Ala Val Tyr Ala Arg Ile Gly Arg Ile Cys Leu Asn Asp Asp
    290                 295                 300

Gly Gly His Cys Cys Leu Val Asn Lys Trp Ser Thr Phe Leu Lys Ala
305                 310                 315                 320

Arg Leu Val Cys Ser Val Pro Gly Glu Asp Gly Ile Glu Thr His Phe
                325                 330                 335

Asp Glu Leu Gln Asp Val Phe Val Gln Gln Thr Gln Asp Val Arg Asn
            340                 345                 350

Pro Val Ile Tyr Ala Val Phe Thr Ser Ser Gly Ser Val Phe Arg Gly
        355                 360                 365
```

```
Ser Ala Val Cys Val Tyr Ser Met Ala Asp Ile Arg Met Val Phe Asn
    370                 375                 380

Gly Pro Phe Ala His Lys Glu Gly Pro Asn Tyr Gln Trp Met Pro Phe
385                 390                 395                 400

Ser Gly Lys Met Pro Tyr Pro Arg Pro Gly Thr Cys Pro Gly Gly Thr
                405                 410                 415

Phe Thr Pro Ser Met Lys Ser Thr Lys Asp Tyr Pro Asp Glu Val Ile
            420                 425                 430

Asn Phe Met Arg Ser His Pro Leu Met Tyr Gln Ala Val Tyr Pro Leu
        435                 440                 445

Gln Arg Arg Pro Leu Val Val Arg Thr Gly Ala Pro Tyr Arg Leu Thr
    450                 455                 460

Thr Ile Ala Val Asp Gln Val Asp Ala Gly Asp Gly Arg Tyr Glu Val
465                 470                 475                 480

Leu Phe Leu Gly Thr Asp Arg Gly Thr Val Gln Lys Val Ile Val Leu
                485                 490                 495

Pro Lys Asp Asp Gln Glu Met Glu Glu Leu Met Leu Glu Glu Val Glu
            500                 505                 510

Val Phe Lys Asp Pro Ala Pro Val Lys Thr Met Thr Ile Ser Ser Lys
        515                 520                 525

Arg Gln Gln Leu Tyr Val Ala Ser Ala Val Gly Val Thr His Leu Ser
    530                 535                 540

Leu His Arg Cys Gln Ala Tyr Gly Ala Ala Cys Ala Asp Cys Cys Leu
545                 550                 555                 560

Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Gln Ala Cys Ser Arg Tyr
                565                 570                 575

Thr Ala Ser Ser Lys Arg Arg Ser Arg Arg Gln Asp Val Arg His Gly
            580                 585                 590

Asn Pro Ile Arg Gln Cys Arg Gly Phe Asn Ser Asn Ala Asn Lys Asn
        595                 600                 605

Ala Val Glu Ser Val Gln Tyr Gly Val Ala Gly Ser Ala Ala Phe Leu
    610                 615                 620
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Glu Cys Gln Pro Arg Ser Pro Gln Ala Thr Val Lys Trp Leu Phe Gln
625 630 635 640

Arg Asp Pro Gly Asp Arg Arg Arg Glu Ile Arg Ala Glu Asp Arg Phe
645 650 655

Leu Arg Thr Glu Gln Gly Leu Leu Leu Arg Ala Leu Gln Leu Ser Asp
660 665 670

Arg Gly Leu Tyr Ser Cys Thr Ala Thr Glu Asn Asn Phe Lys His Val
675 680 685

Val Thr Arg Val Gln Leu His Val Leu Gly Arg Asp Ala Val His Ala
690 695 700

Ala Leu Phe Pro Pro Leu Ser Met Ser Ala Pro Pro Pro Pro Gly Ala
705 710 715 720

Gly Pro Pro Thr Pro Pro Tyr Gln Glu Leu Ala Gln Leu Leu Ala Gln
725 730 735

Pro Glu Val Gly Leu Ile His Gln Tyr Cys Gln Gly Tyr Trp Arg His
740 745 750

Val Pro Pro Ser Pro Arg Glu Ala Pro Gly Ala Pro Arg Ser Pro Glu
755 760 765

Pro Gln Asp Gln Lys Lys Pro Arg Asn Arg Arg His His Pro Pro Asp
770 775 780

Thr
785

<210> 19

<211> 649

<212> DNA

<213> Homo sapiens

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<221> CDS

<222> (17)..(592)

<220>

<221> misc_feature

<222> (17)..(94)

<223> Signal peptide

<400> 19

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                  1               5                   10

gcc ttg ctg ctc tac ctc cac cat gcc aag tgg tcc cag gct gca ccc       100
Ala Leu Leu Leu Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro
        15                  20                  25

atg gca gaa gga gga ggg cag aat cat cac gaa gtg gtg aag ttc atg       148
Met Ala Glu Gly Gly Gly Gln Asn His His Glu Val Val Lys Phe Met
    30                  35                  40

gat gtc tat cag cgc agc tac tgc cat cca atc gag acc ctg gtg gac       196
Asp Val Tyr Gln Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp
45                  50                  55                  60

atc ttc cag gag tac cct gat gag atc gag tac atc ttc aag cca tcc       244
Ile Phe Gln Glu Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser
                65                  70                  75

tgt gtg ccc ctg atg cga tgc ggg ggc tgc tgc aat gac gag ggc ctg       292
Cys Val Pro Leu Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu
            80                  85                  90

gag tgt gtg ccc act gag gag tcc aac atc acc atg cag att atg cgg       340
Glu Cys Val Pro Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg
        95                  100                 105

atc aaa cct cac caa ggc cag cac ata gga gag atg agc ttc cta cag       388
Ile Lys Pro His Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln
    110                 115                 120

cac aac aaa tgt gaa tgc aga cca aag aaa gat aga gca aga caa gaa       436
His Asn Lys Cys Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu
125                 130                 135                 140

aat ccc tgt ggg cct tgc tca gag cgg aga aag cat ttg ttt gta caa       484
Asn Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln
                145                 150                 155

gat ccg cag acg tgt aaa tgt tcc tgc aaa aac aca gac tcg cgt tgc       532
Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser Arg Cys
            160                 165                 170

aag gcg agg cag ctt gag tta aac gaa cgt act tgc aga tgt gac aag       580
Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys
        175                 180                 185

ccg agg cgg tga gccgggcagg aggaaggagc ctccctcagc gtttcgggaa           632
Pro Arg Arg
    190
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ccagatctct caccagg 649

<210> 20

<211> 191

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (17)..(94)

<223> Signal peptide

<400> 20

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Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu
1               5                   10                  15

Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly
            20                  25                  30

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln
        35                  40                  45

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu
    50                  55                  60

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu
65                  70                  75                  80

Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu Glu Cys Val Pro
                85                  90                  95

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His
            100                 105                 110

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys
        115                 120                 125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly
    130                 135                 140

Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr
145                 150                 155                 160
```

```
Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser Arg Cys Lys Ala Arg Gln
                165                 170                 175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg
            180                 185                 190
```

<210> 21

<211> 755

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (5)..(628)

<400> 21

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cacc atg agc cct ctg ctc cgc cgc ctg ctg ctc gcc gca ctc ctg cag      49
     Met Ser Pro Leu Leu Arg Arg Leu Leu Leu Ala Ala Leu Leu Gln
     1               5                   10                  15

ctg gcc ccc gcc cag gcc cct gtc tcc cag cct gat gcc cct ggc cac      97
Leu Ala Pro Ala Gln Ala Pro Val Ser Gln Pro Asp Ala Pro Gly His
                20                  25                  30

cag agg aaa gtg gtg tca tgg ata gat gtg tat act cgc gct acc tgc     145
Gln Arg Lys Val Val Ser Trp Ile Asp Val Tyr Thr Arg Ala Thr Cys
            35                  40                  45

cag ccc cgg gag gtg gtg gtg ccc ttg act gtg gag ctc atg ggc acc     193
Gln Pro Arg Glu Val Val Val Pro Leu Thr Val Glu Leu Met Gly Thr
        50                  55                  60

gtg gcc aaa cag ctg gtg ccc agc tgc gtg act gtg cag cgc tgt ggt     241
Val Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly
    65                  70                  75

ggc tgc tgc cct gac gat ggc ctg gag tgt gtg ccc act ggg cag cac     289
Gly Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His
80                  85                  90                  95

caa gtc cgg atg cag atc ctc atg atc cgg tac ccg agc agt cag ctg     337
Gln Val Arg Met Gln Ile Leu Met Ile Arg Tyr Pro Ser Ser Gln Leu
                100                 105                 110

ggg gag atg tcc ctg gaa gaa cac agc cag tgt gaa tgc aga cct aaa     385
Gly Glu Met Ser Leu Glu Glu His Ser Gln Cys Glu Cys Arg Pro Lys
            115                 120                 125

aaa aag gac agt gct gtg aag cca gac agg gct gcc act ccc cac cac     433
Lys Lys Asp Ser Ala Val Lys Pro Asp Arg Ala Ala Thr Pro His His
```

```
        130                 135                 140

cgt ccc cag ccc cgt tct gtt ccg ggc tgg gac tct gcc ccc gga gca     481
Arg Pro Gln Pro Arg Ser Val Pro Gly Trp Asp Ser Ala Pro Gly Ala
    145                 150                 155

ccc tcc cca gct gac atc acc cat ccc act cca gcc cca ggc ccc tct     529
Pro Ser Pro Ala Asp Ile Thr His Pro Thr Pro Ala Pro Gly Pro Ser
160                 165                 170                 175

gcc cac gct gca ccc agc acc acc agc gcc ctg acc ccc gga cct gcc     577
Ala His Ala Ala Pro Ser Thr Thr Ser Ala Leu Thr Pro Gly Pro Ala
                180                 185                 190

gcc gcc gct gcc gac gcc gca gct tcc tcc gtt gcc aag ggc ggg gct     625
Ala Ala Ala Ala Asp Ala Ala Ala Ser Ser Val Ala Lys Gly Gly Ala
            195                 200                 205

tag agctcaaccc agacacctgc aggtgccgga agctgcgaag gtgacacatg          678

gcttttcaga ctcagcaggg tgacttgcct cagaggctat atcccagtgg gggaacaaag   738

aggagcctgg taaaaaa                                                  755


<210>  22

<211>  207

<212>  PRT

<213>  Homo sapiens


<400>  22

Met Ser Pro Leu Leu Arg Arg Leu Leu Leu Ala Ala Leu Leu Gln Leu
1               5                   10                  15

Ala Pro Ala Gln Ala Pro Val Ser Gln Pro Asp Ala Pro Gly His Gln
            20                  25                  30

Arg Lys Val Val Ser Trp Ile Asp Val Tyr Thr Arg Ala Thr Cys Gln
        35                  40                  45

Pro Arg Glu Val Val Val Pro Leu Thr Val Glu Leu Met Gly Thr Val
    50                  55                  60

Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly Gly
65                  70                  75                  80

Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His Gln
                85                  90                  95

Val Arg Met Gln Ile Leu Met Ile Arg Tyr Pro Ser Ser Gln Leu Gly
            100                 105                 110
```

```
Glu Met Ser Leu Glu Glu His Ser Gln Cys Glu Cys Arg Pro Lys Lys
        115                 120                 125

Lys Asp Ser Ala Val Lys Pro Asp Arg Ala Ala Thr Pro His His Arg
    130                 135                 140

Pro Gln Pro Arg Ser Val Pro Gly Trp Asp Ser Ala Pro Gly Ala Pro
145                 150                 155                 160

Ser Pro Ala Asp Ile Thr His Pro Thr Pro Ala Pro Gly Pro Ser Ala
                165                 170                 175

His Ala Ala Pro Ser Thr Thr Ser Ala Leu Thr Pro Gly Pro Ala Ala
            180                 185                 190

Ala Ala Ala Asp Ala Ala Ala Ser Ser Val Ala Lys Gly Gly Ala
        195                 200                 205
```

<210> 23

<211> 1997

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (352)..(1611)

<400> 23

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cccgccccgc ctctccaaaa agctacaccg acgcggaccg cggcggcgtc ctccctcgcc      60

ctcgcttcac ctcgcgggct ccgaatgcgg ggagctcgga tgtccggttt cctgtgaggc     120

ttttacctga cacccgccgc ctttccccgg cactggctgg gagggcgccc tgcaaagttg     180

ggaacgcgga gccccggacc cgctcccgcc gcctccggct cgcccagggg gggtcgccgg     240

gaggagcccg ggggagaggg accaggaggg gcccgcggcc tcgcaggggc gcccgcgccc     300

ccacccctgc ccccgccagc ggaccggtcc cccacccccg gtccttccac c atg cac      357
                                                         Met His
                                                         1

ttg ctg ggc ttc ttc tct gtg gcg tgt tct ctg ctc gcc gct gcg ctg       405
Leu Leu Gly Phe Phe Ser Val Ala Cys Ser Leu Leu Ala Ala Ala Leu
    5                   10                  15

ctc ccg ggt cct cgc gag gcg ccc gcc gcc gcc gcc gcc ttc gag tcc       453
```

```
Leu Pro Gly Pro Arg Glu Ala Pro Ala Ala Ala Ala Ala Phe Glu Ser
    20                  25                  30

gga ctc gac ctc tcg gac gcg gag ccc gac gcg ggc gag gcc acg gct      501
Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala Thr Ala
35                  40                  45                  50

tat gca agc aaa gat ctg gag gag cag tta cgg tct gtg tcc agt gta      549
Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser Ser Val
                55                  60                  65

gat gaa ctc atg act gta ctc tac cca gaa tat tgg aaa atg tac aag      597
Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met Tyr Lys
            70                  75                  80

tgt cag cta agg aaa gga ggc tgg caa cat aac aga gaa cag gcc aac      645
Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln Ala Asn
        85                  90                  95

ctc aac tca agg aca gaa gag act ata aaa ttt gct gca gca cat tat      693
Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala His Tyr
    100                 105                 110

aat aca gag atc ttg aaa agt att gat aat gag tgg aga aag act caa      741
Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys Thr Gln
115                 120                 125                 130

tgc atg cca cgg gag gtg tgt ata gat gtg ggg aag gag ttt gga gtc      789
Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe Gly Val
                135                 140                 145

gcg aca aac acc ttc ttt aaa cct cca tgt gtg tcc gtc tac aga tgt      837
Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr Arg Cys
            150                 155                 160

ggg ggt tgc tgc aat agt gag ggg ctg cag tgc atg aac acc agc acg      885
Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr Ser Thr
        165                 170                 175

agc tac ctc agc aag acg tta ttt gaa att aca gtg cct ctc tct caa      933
Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu Ser Gln
    180                 185                 190

ggc ccc aaa cca gta aca atc agt ttt gcc aat cac act tcc tgc cga      981
Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser Cys Arg
195                 200                 205                 210

tgc atg tct aaa ctg gat gtt tac aga caa gtt cat tcc att att aga     1029
Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile Ile Arg
                215                 220                 225

cgt tcc ctg cca gca aca cta cca cag tgt cag gca gcg aac aag acc     1077
Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn Lys Thr
            230                 235                 240

tgc ccc acc aat tac atg tgg aat aat cac atc tgc aga tgc ctg gct     1125
Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys Leu Ala
        245                 250                 255

cag gaa gat ttt atg ttt tcc tcg gat gct gga gat gac tca aca gat     1173
Gln Glu Asp Phe Met Phe Ser Ser Asp Ala Gly Asp Asp Ser Thr Asp
    260                 265                 270
```

```
gga ttc cat gac atc tgt gga cca aac aag gag ctg gat gaa gag acc      1221
Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu Glu Thr
275                 280                 285                 290

tgt cag tgt gtc tgc aga gcg ggg ctt cgg cct gcc agc tgt gga ccc      1269
Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys Gly Pro
                295                 300                 305

cac aaa gaa cta gac aga aac tca tgc cag tgt gtc tgt aaa aac aaa      1317
His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys Asn Lys
            310                 315                 320

ctc ttc ccc agc caa tgt ggg gcc aac cga gaa ttt gat gaa aac aca      1365
Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu Asn Thr
        325                 330                 335

tgc cag tgt gta tgt aaa aga acc tgc ccc aga aat caa ccc cta aat      1413
Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro Leu Asn
    340                 345                 350

cct gga aaa tgt gcc tgt gaa tgt aca gaa agt cca cag aaa tgc ttg      1461
Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys Cys Leu
355                 360                 365                 370

tta aaa gga aag aag ttc cac cac caa aca tgc agc tgt tac aga cgg      1509
Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr Arg Arg
                375                 380                 385

cca tgt acg aac cgc cag aag gct tgt gag cca gga ttt tca tat agt      1557
Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser Tyr Ser
            390                 395                 400

gaa gaa gtg tgt cgt tgt gtc cct tca tat tgg aaa aga cca caa atg      1605
Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro Gln Met
        405                 410                 415

agc taa gattgtactg ttttccagtt catcgatttt ctattatgga aaactgtgtt       1661
Ser

gccacagtag aactgtctgt gaacagagag acccttgtgg gtccatgcta acaaagacaa    1721

aagtctgtct ttcctgaacc atgtggataa ctttacagaa atggactgga gctcatctgc    1781

aaaaggcctc ttgtaaagac tggttttctg ccaatgacca aacagccaag attttcctct    1841

tgtgatttct ttaaaagaat gactatataa tttatttcca ctaaaaatat tgtttctgca    1901

ttcattttta tagcaacaac aattggtaaa actcactgtg atcaatattt ttatatcatg    1961

caaaatatgt ttaaaataaa atgaaaattg tattat                              1997
```

<210> 24

<211> 419

<212> PRT

<213> Homo sapiens

<400> 24

Met His Leu Leu Gly Phe Phe Ser Val Ala Cys Ser Leu Leu Ala Ala
1 5 10 15

Ala Leu Leu Pro Gly Pro Arg Glu Ala Pro Ala Ala Ala Ala Ala Phe
20 25 30

Glu Ser Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala
35 40 45

Thr Ala Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser
50 55 60

Ser Val Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met
65 70 75 80

Tyr Lys Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln
85 90 95

Ala Asn Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala
100 105 110

His Tyr Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys
115 120 125

Thr Gln Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe
130 135 140

Gly Val Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr
145 150 155 160

Arg Cys Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr
165 170 175

Ser Thr Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu
180 185 190

Ser Gln Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser
195 200 205

Cys Arg Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile
210 215 220

Ile Arg Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn
225 230 235 240

Lys Thr Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys
245 250 255

Leu Ala Gln Glu Asp Phe Met Phe Ser Ser Asp Ala Gly Asp Asp Ser
260 265 270

Thr Asp Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu
275 280 285

Glu Thr Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys
290 295 300

Gly Pro His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys
305 310 315 320

Asn Lys Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu
325 330 335

Asn Thr Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro
340 345 350

Leu Asn Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys
355 360 365

Cys Leu Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr
370 375 380

Arg Arg Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser
385 390 395 400

Tyr Ser Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro
405 410 415

Gln Met Ser

<210> 25

<211> 2029

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (411)..(1475)

<400> 25

gttgggttcc agctttctgt agctgtaagc attggtggcc acaccacctc cttacaaagc 60

aactagaacc tgcggcatac attggagaga ttttttaat tttctggaca tgaagtaaat 120

ttagagtgct ttctaatttc aggtagaaga catgtccacc ttctgattat ttttggagaa 180

cattttgatt tttttcatct ctctctcccc acccctaaga ttgtgcaaaa aaagcgtacc 240

ttgcctaatt gaaataattt cattggattt tgatcagaac tgattatttg gttttctgtg 300

tgaagttttg aggtttcaaa ctttccttct ggagaatgcc ttttgaaaca attttctcta 360

gctgcctgat gtcaactgct tagtaatcag tggatattga aatattcaaa atg tac 416
Met Tyr
1

aga gag tgg gta gtg gtg aat gtt ttc atg atg ttg tac gtc cag ctg 464
Arg Glu Trp Val Val Val Asn Val Phe Met Met Leu Tyr Val Gln Leu
5 10 15

gtg cag ggc tcc agt aat gaa cat gga cca gtg aag cga tca tct cag 512
Val Gln Gly Ser Ser Asn Glu His Gly Pro Val Lys Arg Ser Ser Gln
20 25 30

tcc aca ttg gaa cga tct gaa cag cag atc agg gct gct tct agt ttg 560
Ser Thr Leu Glu Arg Ser Glu Gln Gln Ile Arg Ala Ala Ser Ser Leu
35 40 45 50

gag gaa cta ctt cga att act cac tct gag gac tgg aag ctg tgg aga 608
Glu Glu Leu Leu Arg Ile Thr His Ser Glu Asp Trp Lys Leu Trp Arg
55 60 65

tgc agg ctg agg ctc aaa agt ttt acc agt atg gac tct cgc tca gca 656
Cys Arg Leu Arg Leu Lys Ser Phe Thr Ser Met Asp Ser Arg Ser Ala
70 75 80

tcc cat cgg tcc act agg ttt gcg gca act ttc tat gac att gaa aca 704
Ser His Arg Ser Thr Arg Phe Ala Ala Thr Phe Tyr Asp Ile Glu Thr
85 90 95

cta aaa gtt ata gat gaa gaa tgg caa aga act cag tgc agc cct aga 752
Leu Lys Val Ile Asp Glu Glu Trp Gln Arg Thr Gln Cys Ser Pro Arg
100 105 110

gaa acg tgc gtg gag gtg gcc agt gag ctg ggg aag agt acc aac aca 800
Glu Thr Cys Val Glu Val Ala Ser Glu Leu Gly Lys Ser Thr Asn Thr
115 120 125 130

ttc ttc aag ccc cct tgt gtg aac gtg ttc cga tgt ggt ggc tgt tgc 848
Phe Phe Lys Pro Pro Cys Val Asn Val Phe Arg Cys Gly Gly Cys Cys
135 140 145

aat gaa gag agc ctt atc tgt atg aac acc agc acc tcg tac att tcc 896
Asn Glu Glu Ser Leu Ile Cys Met Asn Thr Ser Thr Ser Tyr Ile Ser
150 155 160

aaa cag ctc ttt gag ata tca gtg cct ttg aca tca gta cct gaa tta 944
Lys Gln Leu Phe Glu Ile Ser Val Pro Leu Thr Ser Val Pro Glu Leu

165 170 175

gtg cct gtt aaa gtt gcc aat cat aca ggt tgt aag tgc ttg cca aca 992
Val Pro Val Lys Val Ala Asn His Thr Gly Cys Lys Cys Leu Pro Thr
180 185 190

gcc ccc cgc cat cca tac tca att atc aga aga tcc atc cag atc cct 1040
Ala Pro Arg His Pro Tyr Ser Ile Ile Arg Arg Ser Ile Gln Ile Pro
195 200 205 210

gaa gaa gat cgc tgt tcc cat tcc aag aaa ctc tgt cct att gac atg 1088
Glu Glu Asp Arg Cys Ser His Ser Lys Lys Leu Cys Pro Ile Asp Met
215 220 225

cta tgg gat agc aac aaa tgt aaa tgt gtt ttg cag gag gaa aat cca 1136
Leu Trp Asp Ser Asn Lys Cys Lys Cys Val Leu Gln Glu Glu Asn Pro
230 235 240

ctt gct gga aca gaa gac cac tct cat ctc cag gaa cca gct ctc tgt 1184
Leu Ala Gly Thr Glu Asp His Ser His Leu Gln Glu Pro Ala Leu Cys
245 250 255

ggg cca cac atg atg ttt gac gaa gat cgt tgc gag tgt gtc tgt aaa 1232
Gly Pro His Met Met Phe Asp Glu Asp Arg Cys Glu Cys Val Cys Lys
260 265 270

aca cca tgt ccc aaa gat cta atc cag cac ccc aaa aac tgc agt tgc 1280
Thr Pro Cys Pro Lys Asp Leu Ile Gln His Pro Lys Asn Cys Ser Cys
275 280 285 290

ttt gag tgc aaa gaa agt ctg gag acc tgc tgc cag aag cac aag cta 1328
Phe Glu Cys Lys Glu Ser Leu Glu Thr Cys Cys Gln Lys His Lys Leu
295 300 305

ttt cac cca gac acc tgc agc tgt gag gac aga tgc ccc ttt cat acc 1376
Phe His Pro Asp Thr Cys Ser Cys Glu Asp Arg Cys Pro Phe His Thr
310 315 320

aga cca tgt gca agt ggc aaa aca gca tgt gca aag cat tgc cgc ttt 1424
Arg Pro Cys Ala Ser Gly Lys Thr Ala Cys Ala Lys His Cys Arg Phe
325 330 335

cca aag gag aaa agg gct gcc cag ggg ccc cac agc cga aag aat cct 1472
Pro Lys Glu Lys Arg Ala Ala Gln Gly Pro His Ser Arg Lys Asn Pro
340 345 350

tga ttcagcgttc caagttcccc atccctgtca tttttaacag catgctgctt 1525

tgccaagttg ctgtcactgt ttttttccca ggtgttaaaa aaaaaatcca ttttacacag 1585

caccacagtg aatccagacc aaccttccat tcacaccagc taaggagtcc ctggttcatt 1645

gatggatgtc ttctagctgc agatgcctct gcgcaccaag gaatggagag gaggggaccc 1705

atgtaatcct tttgtttagt tttgtttttg ttttttggtg aatgagaaag gtgtgctggt 1765

catggaatgg caggtgtcat atgactgatt actcagagca gatgaggaaa actgtagtct 1825

ctgagtcctt tgctaatcgc aactcttgtg aattattctg attctttttt atgcagaatt 1885

tgattcgtat gatcagtact gactttctga ttactgtcca gcttatagtc ttccagttta 1945

atgaactacc atctgatgtt tcatatttaa gtgtatttaa agaaaataaa caccattatt 2005

caagccaaaa aaaaaaaaaa aaaa 2029

<210> 26

<211> 354

<212> PRT

<213> Homo sapiens

<400> 26

Met Tyr Arg Glu Trp Val Val Val Asn Val Phe Met Met Leu Tyr Val
1 5 10 15

Gln Leu Val Gln Gly Ser Ser Asn Glu His Gly Pro Val Lys Arg Ser
20 25 30

Ser Gln Ser Thr Leu Glu Arg Ser Glu Gln Gln Ile Arg Ala Ala Ser
35 40 45

Ser Leu Glu Glu Leu Leu Arg Ile Thr His Ser Glu Asp Trp Lys Leu
50 55 60

Trp Arg Cys Arg Leu Arg Leu Lys Ser Phe Thr Ser Met Asp Ser Arg
65 70 75 80

Ser Ala Ser His Arg Ser Thr Arg Phe Ala Ala Thr Phe Tyr Asp Ile
85 90 95

Glu Thr Leu Lys Val Ile Asp Glu Glu Trp Gln Arg Thr Gln Cys Ser
100 105 110

Pro Arg Glu Thr Cys Val Glu Val Ala Ser Glu Leu Gly Lys Ser Thr
115 120 125

Asn Thr Phe Phe Lys Pro Pro Cys Val Asn Val Phe Arg Cys Gly Gly
130 135 140

Cys Cys Asn Glu Glu Ser Leu Ile Cys Met Asn Thr Ser Thr Ser Tyr
145 150 155 160

Ile Ser Lys Gln Leu Phe Glu Ile Ser Val Pro Leu Thr Ser Val Pro
165 170 175

Glu Leu Val Pro Val Lys Val Ala Asn His Thr Gly Cys Lys Cys Leu

```
            180                 185                 190

Pro Thr Ala Pro Arg His Pro Tyr Ser Ile Ile Arg Arg Ser Ile Gln
        195                 200                 205

Ile Pro Glu Glu Asp Arg Cys Ser His Ser Lys Lys Leu Cys Pro Ile
    210                 215                 220

Asp Met Leu Trp Asp Ser Asn Lys Cys Lys Cys Val Leu Gln Glu Glu
225                 230                 235                 240

Asn Pro Leu Ala Gly Thr Glu Asp His Ser His Leu Gln Glu Pro Ala
                245                 250                 255

Leu Cys Gly Pro His Met Met Phe Asp Glu Asp Arg Cys Glu Cys Val
            260                 265                 270

Cys Lys Thr Pro Cys Pro Lys Asp Leu Ile Gln His Pro Lys Asn Cys
        275                 280                 285

Ser Cys Phe Glu Cys Lys Glu Ser Leu Glu Thr Cys Cys Gln Lys His
    290                 295                 300

Lys Leu Phe His Pro Asp Thr Cys Ser Cys Glu Asp Arg Cys Pro Phe
305                 310                 315                 320

His Thr Arg Pro Cys Ala Ser Gly Lys Thr Ala Cys Ala Lys His Cys
                325                 330                 335

Arg Phe Pro Lys Glu Lys Arg Ala Ala Gln Gly Pro His Ser Arg Lys
            340                 345                 350

Asn Pro
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<210> 27

<211> 1645

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (322)..(771)

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<400>  27
gggattcggg ccgcccagct acgggaggac ctggagtggc actgggcgcc cgacggacca      60

tccccgggac ccgcctgccc ctcggcgccc cgccccgccg ggccgctccc cgtcgggttc     120

cccagccaca gccttaccta cgggctcctg actccgcaag gcttccagaa gatgctcgaa     180

ccaccggccg gggcctcggg gcagcagtga gggaggcgtc cagcccccca ctcagctctt     240

ctcctcctgt gccaggggct ccccgggga tgagcatggt ggtttccct cggagccccc       300

tggctcggga cgtctgagaa g atg ccg gtc atg agg ctg ttc cct tgc ttc       351
                        Met Pro Val Met Arg Leu Phe Pro Cys Phe
                        1               5                   10

ctg cag ctc ctg gcc ggg ctg gcg ctg cct gct gtg ccc ccc cag cag       399
Leu Gln Leu Leu Ala Gly Leu Ala Leu Pro Ala Val Pro Pro Gln Gln
                15                  20                  25

tgg gcc ttg tct gct ggg aac ggc tcg tca gag gtg gaa gtg gta ccc       447
Trp Ala Leu Ser Ala Gly Asn Gly Ser Ser Glu Val Glu Val Val Pro
            30                  35                  40

ttc cag gaa gtg tgg ggc cgc agc tac tgc cgg gcg ctg gag agg ctg       495
Phe Gln Glu Val Trp Gly Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu
        45                  50                  55

gtg gac gtc gtg tcc gag tac ccc agc gag gtg gag cac atg ttc agc       543
Val Asp Val Val Ser Glu Tyr Pro Ser Glu Val Glu His Met Phe Ser
    60                  65                  70

cca tcc tgt gtc tcc ctg ctg cgc tgc acc ggc tgc tgc ggc gat gag       591
Pro Ser Cys Val Ser Leu Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu
75                  80                  85                  90

aat ctg cac tgt gtg ccg gtg gag acg gcc aat gtc acc atg cag ctc       639
Asn Leu His Cys Val Pro Val Glu Thr Ala Asn Val Thr Met Gln Leu
                95                  100                 105

cta aag atc cgt tct ggg gac cgg ccc tcc tac gtg gag ctg acg ttc       687
Leu Lys Ile Arg Ser Gly Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe
            110                 115                 120

tct cag cac gtt cgc tgc gaa tgc cgg cct ctg cgg gag aag atg aag       735
Ser Gln His Val Arg Cys Glu Cys Arg Pro Leu Arg Glu Lys Met Lys
        125                 130                 135

ccg gaa agg tgc ggc gat gct gtt ccc cgg agg taa cccacccctt            781
Pro Glu Arg Cys Gly Asp Ala Val Pro Arg Arg
    140                 145

ggaggagaga gaccccgcac ccggctcgtg tatttattac cgtcacactc ttcagtgact     841

cctgctggta cctgccctct atttattagc caactgtttc cctgctgaat gcctcgctcc     901

cttcaagacg aggggcaggg aaggacagga ccctcaggaa ttcagtgcct tcaacaacgt     961

gagagaaaga gagaagccag ccacagaccc ctgggagctt ccgctttgaa agaagcaaga    1021

cacgtggcct cgtgaggggc aagctaggcc ccagaggccc tggaggtctc caggggcctg    1081

cagaaggaaa gaagggggcc ctgctacctg ttcttgggcc tcaggctctg cacagacaag    1141
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cagccccttgc tttcggagct cctgtccaaa gtagggatgc ggattctgct ggggccgcca 1201

cggcctggtg gtgggaaggc cggcagcggg cggaggggat tcagccactt ccccctcttc 1261

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ttccggccga ggtgccacca ccctgccccc actaagagac acatacagag tgggccccgg 1441

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<212> PRT

<213> Homo sapiens

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Leu Ala Leu Pro Ala Val Pro Pro Gln Gln Trp Ala Leu Ser Ala Gly
            20                  25                  30

Asn Gly Ser Ser Glu Val Glu Val Val Pro Phe Gln Glu Val Trp Gly
        35                  40                  45

Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu
    50                  55                  60

Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu
65                  70                  75                  80

Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro
                85                  90                  95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly
            100                 105                 110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys
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Ala Val Pro Arg Arg
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<222>  (304)..(4374)


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ccggcacccg cagacgcccc tgcagccgcc ggtcggcgcc cgggctccct agccctgtgc     180

gctcaactgt cctgcgctgc ggggtgccgc gagttccacc tccgcgcctc cttctctaga     240

caggcgctgg gagaaagaac cggctcccga gttctgggca tttcgcccgg ctcgaggtgc     300

agg atg cag agc aag gtg ctg ctg gcc gtc gcc ctg tgg ctc tgc gtg       348
    Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val
    1               5                   10                  15

gag acc cgg gcc gcc tct gtg ggt ttg cct agt gtt tct ctt gat ctg       396
Glu Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu
                20                  25                  30


ccc agg ctc agc ata caa aaa gac ata ctt aca att aag gct aat aca       444
Pro Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr
            35                  40                  45

act ctt caa att act tgc agg gga cag agg gac ttg gac tgg ctt tgg       492
Thr Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp
        50                  55                  60

ccc aat aat cag agt ggc agt gag caa agg gtg gag gtg act gag tgc       540
Pro Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys
    65                  70                  75

agc gat ggc ctc ttc tgt aag aca ctc aca att cca aaa gtg atc gga       588
Ser Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly
80                  85                  90                  95

aat gac act gga gcc tac aag tgc ttc tac cgg gaa act gac ttg gcc       636
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Asn Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala
100 105 110

tcg gtc att tat gtc tat gtt caa gat tac aga tct cca ttt att gct 684
Ser Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala
115 120 125

tct gtt agt gac caa cat gga gtc gtg tac att act gag aac aaa aac 732
Ser Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn
130 135 140

aaa act gtg gtg att cca tgt ctc ggg tcc att tca aat ctc aac gtg 780
Lys Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val
145 150 155

tca ctt tgt gca aga tac cca gaa aag aga ttt gtt cct gat ggt aac 828
Ser Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn
160 165 170 175

aga att tcc tgg gac agc aag aag ggc ttt act att ccc agc tac atg 876
Arg Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met
180 185 190

atc agc tat gct ggc atg gtc ttc tgt gaa gca aaa att aat gat gaa 924
Ile Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu
195 200 205

agt tac cag tct att atg tac ata gtt gtc gtt gta ggg tat agg att 972
Ser Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile
210 215 220

tat gat gtg gtt ctg agt ccg tct cat gga att gaa cta tct gtt gga 1020
Tyr Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly
225 230 235

gaa aag ctt gtc tta aat tgt aca gca aga act gaa cta aat gtg ggg 1068
Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly
240 245 250 255

att gac ttc aac tgg gaa tac cct tct tcg aag cat cag cat aag aaa 1116
Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys
260 265 270

ctt gta aac cga gac cta aaa acc cag tct ggg agt gag atg aag aaa 1164
Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys
275 280 285

ttt ttg agc acc tta act ata gat ggt gta acc cgg agt gac caa gga 1212
Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly
290 295 300

ttg tac acc tgt gca gca tcc agt ggg ctg atg acc aag aag aac agc 1260
Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser
305 310 315

aca ttt gtc agg gtc cat gaa aaa cct ttt gtt gct ttt gga agt ggc 1308
Thr Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly
320 325 330 335

atg gaa tct ctg gtg gaa gcc acg gtg ggg gag cgt gtc aga atc cct 1356
Met Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro

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                340                     345                     350

gcg aag tac ctt ggt tac cca ccc cca gaa ata aaa tgg tat aaa aat      1404
Ala Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn
            355                 360                 365

gga ata ccc ctt gag tcc aat cac aca att aaa gcg ggg cat gta ctg      1452
Gly Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu
        370                 375                 380

acg att atg gaa gtg agt gaa aga gac aca gga aat tac act gtc atc      1500
Thr Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile
    385                 390                 395

ctt acc aat ccc att tca aag gag aag cag agc cat gtg gtc tct ctg      1548
Leu Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu
400                 405                 410                 415

gtt gtg tat gtc cca ccc cag att ggt gag aaa tct cta atc tct cct      1596
Val Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro
                420                 425                 430

gtg gat tcc tac cag tac ggc acc act caa acg ctg aca tgt acg gtc      1644
Val Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val
            435                 440                 445

tat gcc att cct ccc ccg cat cac atc cac tgg tat tgg cag ttg gag      1692
Tyr Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu
        450                 455                 460

gaa gag tgc gcc aac gag ccc agc caa gct gtc tca gtg aca aac cca      1740
Glu Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro
    465                 470                 475

tac cct tgt gaa gaa tgg aga agt gtg gag gac ttc cag gga gga aat      1788
Tyr Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn
480                 485                 490                 495

aaa att gaa gtt aat aaa aat caa ttt gct cta att gaa gga aaa aac      1836
Lys Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn
                500                 505                 510

aaa act gta agt acc ctt gtt atc caa gcg gca aat gtg tca gct ttg      1884
Lys Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu
            515                 520                 525

tac aaa tgt gaa gcg gtc aac aaa gtc ggg aga gga gag agg gtg atc      1932
Tyr Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile
        530                 535                 540

tcc ttc cac gtg acc agg ggt cct gaa att act ttg caa cct gac atg      1980
Ser Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met
    545                 550                 555

cag ccc act gag cag gag agc gtg tct ttg tgg tgc act gca gac aga      2028
Gln Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg
560                 565                 570                 575

tct acg ttt gag aac ctc aca tgg tac aag ctt ggc cca cag cct ctg      2076
Ser Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu
                580                 585                 590
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cca atc cat gtg gga gag ttg ccc aca cct gtt tgc aag aac ttg gat      2124
Pro Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp
            595                 600                 605

act ctt tgg aaa ttg aat gcc acc atg ttc tct aat agc aca aat gac      2172
Thr Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp
        610                 615                 620

att ttg atc atg gag ctt aag aat gca tcc ttg cag gac caa gga gac      2220
Ile Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp
    625                 630                 635

tat gtc tgc ctt gct caa gac agg aag acc aag aaa aga cat tgc gtg      2268
Tyr Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val
640                 645                 650                 655

gtc agg cag ctc aca gtc cta gag cgt gtg gca ccc acg atc aca gga      2316
Val Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly
                660                 665                 670

aac ctg gag aat cag acg aca agt att ggg gaa agc atc gaa gtc tca      2364
Asn Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser
            675                 680                 685

tgc acg gca tct ggg aat ccc cct cca cag atc atg tgg ttt aaa gat      2412
Cys Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp
        690                 695                 700

aat gag acc ctt gta gaa gac tca ggc att gta ttg aag gat ggg aac      2460
Asn Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn
    705                 710                 715

cgg aac ctc act atc cgc aga gtg agg aag gag gac gaa ggc ctc tac      2508
Arg Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr
720                 725                 730                 735

acc tgc cag gca tgc agt gtt ctt ggc tgt gca aaa gtg gag gca ttt      2556
Thr Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe
                740                 745                 750

ttc ata ata gaa ggt gcc cag gaa aag acg aac ttg gaa atc att att      2604
Phe Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ile Ile Ile
            755                 760                 765

cta gta ggc acg gcg gtg att gcc atg ttc ttc tgg cta ctt ctt gtc      2652
Leu Val Gly Thr Ala Val Ile Ala Met Phe Phe Trp Leu Leu Leu Val
        770                 775                 780

atc atc cta cgg acc gtt aag cgg gcc aat gga ggg gaa ctg aag aca      2700
Ile Ile Leu Arg Thr Val Lys Arg Ala Asn Gly Gly Glu Leu Lys Thr
    785                 790                 795


ggc tac ttg tcc atc gtc atg gat cca gat gaa ctc cca ttg gat gaa      2748
Gly Tyr Leu Ser Ile Val Met Asp Pro Asp Glu Leu Pro Leu Asp Glu
800                 805                 810                 815

cat tgt gaa cga ctg cct tat gat gcc agc aaa tgg gaa ttc ccc aga      2796
His Cys Glu Arg Leu Pro Tyr Asp Ala Ser Lys Trp Glu Phe Pro Arg
                820                 825                 830

gac cgg ctg aag cta ggt aag cct ctt ggc cgt ggt gcc ttt ggc caa      2844
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Asp Arg Leu Lys Leu Gly Lys Pro Leu Gly Arg Gly Ala Phe Gly Gln
            835                     840                     845

gtg att gaa gca gat gcc ttt gga att gac aag aca gca act tgc agg      2892
Val Ile Glu Ala Asp Ala Phe Gly Ile Asp Lys Thr Ala Thr Cys Arg
        850                     855                     860

aca gta gca gtc aaa atg ttg aaa gaa gga gca aca cac agt gag cat      2940
Thr Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr His Ser Glu His
    865                     870                     875

cga gct ctc atg tct gaa ctc aag atc ctc att cat att ggt cac cat      2988
Arg Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly His His
880                     885                     890                     895

ctc aat gtg gtc aac ctt cta ggt gcc tgt acc aag cca gga ggg cca      3036
Leu Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gly Gly Pro
                900                     905                     910

ctc atg gtg att gtg gaa ttc tgc aaa ttt gga aac ctg tcc act tac      3084
Leu Met Val Ile Val Glu Phe Cys Lys Phe Gly Asn Leu Ser Thr Tyr
            915                     920                     925

ctg agg agc aag aga aat gaa ttt gtc ccc tac aag acc aaa ggg gca      3132
Leu Arg Ser Lys Arg Asn Glu Phe Val Pro Tyr Lys Thr Lys Gly Ala
        930                     935                     940

cga ttc cgt caa ggg aaa gac tac gtt gga gca atc cct gtg gat ctg      3180
Arg Phe Arg Gln Gly Lys Asp Tyr Val Gly Ala Ile Pro Val Asp Leu
    945                     950                     955

aaa cgg cgc ttg gac agc atc acc agt agc cag agc tca gcc agc tct      3228
Lys Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser
960                     965                     970                     975

gga ttt gtg gag gag aag tcc ctc agt gat gta gaa gaa gag gaa gct      3276
Gly Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Glu Ala
                980                     985                     990

cct gaa gat ctg tat aag gac ttc ctg  acc ttg gag cat ctc  atc tgt    3324
Pro Glu Asp Leu Tyr Lys Asp Phe Leu  Thr Leu Glu His Leu  Ile Cys
            995                     1000                      1005

tac agc ttc  caa gtg gct aag ggc  atg gag ttc ttg gca  tcg cga       3369
Tyr Ser Phe  Gln Val Ala Lys Gly  Met Glu Phe Leu Ala  Ser Arg
        1010                  1015                  1020

aag tgt atc  cac agg gac ctg gcg  gca cga aat atc ctc  tta tcg       3414
Lys Cys Ile  His Arg Asp Leu Ala  Ala Arg Asn Ile Leu  Leu Ser
        1025                  1030                  1035

gag aag aac  gtg gtt aaa atc tgt  gac ttt ggc ttg gcc  cgg gat       3459
Glu Lys Asn  Val Val Lys Ile Cys  Asp Phe Gly Leu Ala  Arg Asp
        1040                  1045                  1050

att tat aaa  gat cca gat tat gtc  aga aaa gga gat gct  cgc ctc       3504
Ile Tyr Lys  Asp Pro Asp Tyr Val  Arg Lys Gly Asp Ala  Arg Leu
        1055                  1060                  1065

cct ttg aaa  tgg atg gcc cca gaa  aca att ttt gac aga  gtg tac       3549
Pro Leu Lys  Trp Met Ala Pro Glu  Thr Ile Phe Asp Arg  Val Tyr
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1070 1075 1080

aca atc cag agt gac gtc tgg tct ttt ggt gtt ttg ctg tgg gaa 3594
Thr Ile Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu
1085 1090 1095

ata ttt tcc tta ggt gct tct cca tat cct ggg gta aag att gat 3639
Ile Phe Ser Leu Gly Ala Ser Pro Tyr Pro Gly Val Lys Ile Asp
1100 1105 1110

gaa gaa ttt tgt agg cga ttg aaa gaa gga act aga atg agg gcc 3684
Glu Glu Phe Cys Arg Arg Leu Lys Glu Gly Thr Arg Met Arg Ala
1115 1120 1125

cct gat tat act aca cca gaa atg tac cag acc atg ctg gac tgc 3729
Pro Asp Tyr Thr Thr Pro Glu Met Tyr Gln Thr Met Leu Asp Cys
1130 1135 1140

tgg cac ggg gag ccc agt cag aga ccc acg ttt tca gag ttg gtg 3774
Trp His Gly Glu Pro Ser Gln Arg Pro Thr Phe Ser Glu Leu Val
1145 1150 1155

gaa cat ttg gga aat ctc ttg caa gct aat gct cag cag gat ggc 3819
Glu His Leu Gly Asn Leu Leu Gln Ala Asn Ala Gln Gln Asp Gly
1160 1165 1170

aaa gac tac att gtt ctt ccg ata tca gag act ttg agc atg gaa 3864
Lys Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu Ser Met Glu
1175 1180 1185

gag gat tct gga ctc tct ctg cct acc tca cct gtt tcc tgt atg 3909
Glu Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser Cys Met
1190 1195 1200

gag gag gag gaa gta tgt gac ccc aaa ttc cat tat gac aac aca 3954
Glu Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn Thr
1205 1210 1215

gca gga atc agt cag tat ctg cag aac agt aag cga aag agc cgg 3999
Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
1220 1225 1230

cct gtg agt gta aaa aca ttt gaa gat atc ccg tta gaa gaa cca 4044
Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro
1235 1240 1245

gaa gta aaa gta atc cca gat gac aac cag acg gac agt ggt atg 4089
Glu Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met
1250 1255 1260

gtt ctt gcc tca gaa gag ctg aaa act ttg gaa gac aga acc aaa 4134
Val Leu Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys
1265 1270 1275

tta tct cca tct ttt ggt gga atg gtg ccc agc aaa agc agg gag 4179
Leu Ser Pro Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu
1280 1285 1290

tct gtg gca tct gaa ggc tca aac cag aca agc ggc tac cag tcc 4224
Ser Val Ala Ser Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser
1295 1300 1305

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gga tat cac tcc gat gac aca gac acc acc gtg tac tcc agt gag      4269
Gly Tyr His Ser Asp Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu
        1310                1315                1320

gaa gca gaa ctt tta aag ctg ata gag att gga gtg caa acc ggt      4314
Glu Ala Glu Leu Leu Lys Leu Ile Glu Ile Gly Val Gln Thr Gly
        1325                1330                1335

agc aca gcc cag att ctc cag cct gac tcg ggg acc aca ctg agc      4359
Ser Thr Ala Gln Ile Leu Gln Pro Asp Ser Gly Thr Thr Leu Ser
        1340                1345                1350

tct cct cct gtt taa aaggaagcat ccacacccca actcccggac atcacatgag  4414
Ser Pro Pro Val
        1355

aggtctgctc agattttgaa gtgttgttct ttccaccagc aggaagtagc cgcatttgat   4474

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cctggaagag gcttgtgacc caagaatgtg tctgtgtctt ctcccagtgt tgacctgatc   4594

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tggagagtac tggagcctgc aaatgcattg tgtttgctct ggtggaggtg ggcatggggt   4954

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agctgtgtgt ggtgtcaaag tttcaggaag gattttaccc ttttgttctt ccccctgtcc   5374

ccaacccact ctcaccccgc aacccatcag tattttagtt atttggcctc tactccagta   5434

aacctgattg ggtttgttca ctctctgaat gattattagc cagacttcaa aattatttta   5494

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accatagtgt gaaatgctgg gaacaatgac tataagacat gctatggcac atatatttat   5674

agtctgttta tgtagaaaca aatgtaatat attaaagcct tatatataat gaactttgta   5734

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<212> PRT

<213> Homo sapiens

<400> 30

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20 25 30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
35 40 45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
50 55 60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
65 70 75 80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
85 90 95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
100 105 110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
115 120 125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
130 135 140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
145 150 155 160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
165 170 175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
180 185 190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
195 200 205

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Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
    210                 215                 220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
225                 230                 235                 240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
                245                 250                 255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
            260                 265                 270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
        275                 280                 285

Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
    290                 295                 300

Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
305                 310                 315                 320

Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met
                325                 330                 335

Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala
            340                 345                 350

Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly
        355                 360                 365

Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr
    370                 375                 380

Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu
385                 390                 395                 400

Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val
                405                 410                 415

Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val
            420                 425                 430

Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr
        435                 440                 445

Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu
    450                 455                 460
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Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr
465                 470                 475                 480

Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys
                485                 490                 495

Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys
            500                 505                 510

Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr
        515                 520                 525

Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser
    530                 535                 540

Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln
545                 550                 555                 560

Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser
                565                 570                 575

Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro
            580                 585                 590

Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp Thr
        595                 600                 605

Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp Ile
    610                 615                 620

Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp Tyr
625                 630                 635                 640

Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val Val
                645                 650                 655

Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly Asn
            660                 665                 670

Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser Cys
        675                 680                 685

Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp Asn
    690                 695                 700

Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn Arg
705                 710                 715                 720
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Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr Thr
725 730 735

Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe Phe
740 745 750

Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ile Ile Ile Leu
755 760 765

Val Gly Thr Ala Val Ile Ala Met Phe Phe Trp Leu Leu Leu Val Ile
770 775 780

Ile Leu Arg Thr Val Lys Arg Ala Asn Gly Gly Glu Leu Lys Thr Gly
785 790 795 800

Tyr Leu Ser Ile Val Met Asp Pro Asp Glu Leu Pro Leu Asp Glu His
805 810 815

Cys Glu Arg Leu Pro Tyr Asp Ala Ser Lys Trp Glu Phe Pro Arg Asp
820 825 830

Arg Leu Lys Leu Gly Lys Pro Leu Gly Arg Gly Ala Phe Gly Gln Val
835 840 845

Ile Glu Ala Asp Ala Phe Gly Ile Asp Lys Thr Ala Thr Cys Arg Thr
850 855 860

Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr His Ser Glu His Arg
865 870 875 880

Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly His His Leu
885 890 895

Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gly Gly Pro Leu
900 905 910

Met Val Ile Val Glu Phe Cys Lys Phe Gly Asn Leu Ser Thr Tyr Leu
915 920 925

Arg Ser Lys Arg Asn Glu Phe Val Pro Tyr Lys Thr Lys Gly Ala Arg
930 935 940

Phe Arg Gln Gly Lys Asp Tyr Val Gly Ala Ile Pro Val Asp Leu Lys
945 950 955 960

Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser Gly

965 970 975

Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Glu Ala Pro
980 985 990

Glu Asp Leu Tyr Lys Asp Phe Leu Thr Leu Glu His Leu Ile Cys Tyr
995 1000 1005

Ser Phe Gln Val Ala Lys Gly Met Glu Phe Leu Ala Ser Arg Lys
1010 1015 1020

Cys Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu
1025 1030 1035

Lys Asn Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile
1040 1045 1050

Tyr Lys Asp Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro
1055 1060 1065

Leu Lys Trp Met Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr
1070 1075 1080

Ile Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile
1085 1090 1095

Phe Ser Leu Gly Ala Ser Pro Tyr Pro Gly Val Lys Ile Asp Glu
1100 1105 1110

Glu Phe Cys Arg Arg Leu Lys Glu Gly Thr Arg Met Arg Ala Pro
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Asp Tyr Thr Thr Pro Glu Met Tyr Gln Thr Met Leu Asp Cys Trp
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His Gly Glu Pro Ser Gln Arg Pro Thr Phe Ser Glu Leu Val Glu
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His Leu Gly Asn Leu Leu Gln Ala Asn Ala Gln Gln Asp Gly Lys
1160 1165 1170

Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu Ser Met Glu Glu
1175 1180 1185

Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser Cys Met Glu
1190 1195 1200

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Glu Glu  Glu Val Cys Asp Pro  Lys Phe His Tyr Asp  Asn Thr Ala
    1205                 1210                 1215

Gly Ile  Ser Gln Tyr Leu Gln  Asn Ser Lys Arg Lys  Ser Arg Pro
    1220                 1225                 1230

Val Ser  Val Lys Thr Phe Glu  Asp Ile Pro Leu Glu  Glu Pro Glu
    1235                 1240                 1245

Val Lys  Val Ile Pro Asp Asp  Asn Gln Thr Asp Ser  Gly Met Val
    1250                 1255                 1260

Leu Ala  Ser Glu Glu Leu Lys  Thr Leu Glu Asp Arg  Thr Lys Leu
    1265                 1270                 1275

Ser Pro  Ser Phe Gly Gly Met  Val Pro Ser Lys Ser  Arg Glu Ser
    1280                 1285                 1290

Val Ala  Ser Glu Gly Ser Asn  Gln Thr Ser Gly Tyr  Gln Ser Gly
    1295                 1300                 1305

Tyr His  Ser Asp Asp Thr Asp  Thr Thr Val Tyr Ser  Ser Glu Glu
    1310                 1315                 1320

Ala Glu  Leu Leu Lys Leu Ile  Glu Ile Gly Val Gln  Thr Gly Ser
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Thr Ala  Gln Ile Leu Gln Pro  Asp Ser Gly Thr Thr  Leu Ser Ser
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Pro Pro  Val
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tgg ctc tgc ctg gga ctc ctg gac ggc ctg gtg agt ggc tac tcc atg     100
Trp Leu Cys Leu Gly Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met
             15                  20                  25

acc ccc ccg acc ttg aac atc acg gag gag tca cac gtc atc gac acc     148
Thr Pro Pro Thr Leu Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr
         30                  35                  40

ggt gac agc ctg tcc atc tcc tgc agg gga cag cac ccc ctc gag tgg     196
Gly Asp Ser Leu Ser Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp
     45                  50                  55

gct tgg cca gga gct cag gag gcg cca gcc acc gga gac aag gac agc     244
Ala Trp Pro Gly Ala Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser
 60                  65                  70                  75

gag gac acg ggg gtg gtg cga gac tgc gag ggc aca gac gcc agg ccc     292
Glu Asp Thr Gly Val Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro
                 80                  85                  90

tac tgc aag gtg ttg ctg ctg cac gag gta cat gcc aac gac aca ggc     340
Tyr Cys Lys Val Leu Leu Leu His Glu Val His Ala Asn Asp Thr Gly
             95                 100                 105

agc tac gtc tgc tac tac aag tac atc aag gca cgc atc gag ggc acc     388
Ser Tyr Val Cys Tyr Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr
        110                 115                 120

acg gcc gcc agc tcc tac gtg ttc gtg aga gac ttt gag cag cca ttc     436
Thr Ala Ala Ser Ser Tyr Val Phe Val Arg Asp Phe Glu Gln Pro Phe
    125                 130                 135

atc aac aag cct gac acg ctc ttg gtc aac agg aag gac gcc atg tgg     484
Ile Asn Lys Pro Asp Thr Leu Leu Val Asn Arg Lys Asp Ala Met Trp
140                 145                 150                 155

gtg ccc tgt ctg gtg tcc atc ccc ggc ctc aat gtc acg ctg cgc tcg     532
Val Pro Cys Leu Val Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser
                160                 165                 170

caa agc tcg gtg ctg tgg cca gac ggg cag gag gtg gtg tgg gat gac     580
Gln Ser Ser Val Leu Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp
            175                 180                 185

cgg cgg ggc atg ctc gtg tcc acg cca ctg ctg cac gat gcc ctg tac     628
Arg Arg Gly Met Leu Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr
        190                 195                 200

ctg cag tgc gag acc acc tgg gga gac cag gac ttc ctt tcc aac ccc     676
Leu Gln Cys Glu Thr Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro
    205                 210                 215

ttc ctg gtg cac atc aca ggc aac gag ctc tat gac atc cag ctg ttg     724
Phe Leu Val His Ile Thr Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu
220                 225                 230                 235

ccc agg aag tcg ctg gag ctg ctg gta ggg gag aag ctg gtc ctg aac     772
Pro Arg Lys Ser Leu Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn
                240                 245                 250

tgc acc gtg tgg gct gag ttt aac tca ggt gtc acc ttt gac tgg gac     820
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Cys Thr Val Trp Ala Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp
            255                 260                 265

tac cca ggg aag cag gca gag cgg ggt aag tgg gtg ccc gag cga cgc     868
Tyr Pro Gly Lys Gln Ala Glu Arg Gly Lys Trp Val Pro Glu Arg Arg
        270                 275                 280

tcc cag cag acc cac aca gaa ctc tcc agc atc ctg acc atc cac aac     916
Ser Gln Gln Thr His Thr Glu Leu Ser Ser Ile Leu Thr Ile His Asn
    285                 290                 295

gtc agc cag cac gac ctg ggc tcg tat gtg tgc aag gcc aac aac ggc     964
Val Ser Gln His Asp Leu Gly Ser Tyr Val Cys Lys Ala Asn Asn Gly
300                 305                 310                 315

atc cag cga ttt cgg gag agc acc gag gtc att gtg cat gaa aat ccc     1012
Ile Gln Arg Phe Arg Glu Ser Thr Glu Val Ile Val His Glu Asn Pro
                320                 325                 330


ttc atc agc gtc gag tgg ctc aaa gga ccc atc ctg gag gcc acg gca     1060
Phe Ile Ser Val Glu Trp Leu Lys Gly Pro Ile Leu Glu Ala Thr Ala
            335                 340                 345

gga gac gag ctg gtg aag ctg ccc gtg aag ctg gca gcg tac ccc ccg     1108
Gly Asp Glu Leu Val Lys Leu Pro Val Lys Leu Ala Ala Tyr Pro Pro
        350                 355                 360

ccc gag ttc cag tgg tac aag gat gga aag gca ctg tcc ggg cgc cac     1156
Pro Glu Phe Gln Trp Tyr Lys Asp Gly Lys Ala Leu Ser Gly Arg His
    365                 370                 375

agt cca cat gcc ctg gtg ctc aag gag gtg aca gag gcc agc aca ggc     1204
Ser Pro His Ala Leu Val Leu Lys Glu Val Thr Glu Ala Ser Thr Gly
380                 385                 390                 395

acc tac acc ctc gcc ctg tgg aac tcc gct gct ggc ctg agg cgc aac     1252
Thr Tyr Thr Leu Ala Leu Trp Asn Ser Ala Ala Gly Leu Arg Arg Asn
                400                 405                 410

atc agc ctg gag ctg gtg gtg aat gtg ccc ccc cag ata cat gag aag     1300
Ile Ser Leu Glu Leu Val Val Asn Val Pro Pro Gln Ile His Glu Lys
            415                 420                 425

gag gcc tcc tcc ccc agc atc tac tcg cgt cac agc cgc cag gcc ctc     1348
Glu Ala Ser Ser Pro Ser Ile Tyr Ser Arg His Ser Arg Gln Ala Leu
        430                 435                 440

acc tgc acg gcc tac ggg gtg ccc ctg cct ctc agc atc cag tgg cac     1396
Thr Cys Thr Ala Tyr Gly Val Pro Leu Pro Leu Ser Ile Gln Trp His
    445                 450                 455

tgg cgg ccc tgg aca ccc tgc aag atg ttt gcc cag cgt agt ctc cgg     1444
Trp Arg Pro Trp Thr Pro Cys Lys Met Phe Ala Gln Arg Ser Leu Arg
460                 465                 470                 475

cgg cgg cag cag caa gac ctc atg cca cag tgc cgt gac tgg agg gcg     1492
Arg Arg Gln Gln Gln Asp Leu Met Pro Gln Cys Arg Asp Trp Arg Ala
                480                 485                 490

gtg acc acg cag gat gcc gtg aac ccc atc gag agc ctg gac acc tgg     1540
Val Thr Thr Gln Asp Ala Val Asn Pro Ile Glu Ser Leu Asp Thr Trp
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              495                 500                 505

acc gag ttt gtg gag gga aag aat aag act gtg agc aag ctg gtg atc    1588
Thr Glu Phe Val Glu Gly Lys Asn Lys Thr Val Ser Lys Leu Val Ile
        510                 515                 520

cag aat gcc aac gtg tct gcc atg tac aag tgt gtg gtc tcc aac aag    1636
Gln Asn Ala Asn Val Ser Ala Met Tyr Lys Cys Val Val Ser Asn Lys
    525                 530                 535

gtg ggc cag gat gag cgg ctc atc tac ttc tat gtg acc acc atc ccc    1684
Val Gly Gln Asp Glu Arg Leu Ile Tyr Phe Tyr Val Thr Thr Ile Pro
540                 545                 550                 555

gac ggc ttc acc atc gaa tcc aag cca tcc gag gag cta cta gag ggc    1732
Asp Gly Phe Thr Ile Glu Ser Lys Pro Ser Glu Glu Leu Leu Glu Gly
                560                 565                 570

cag ccg gtg ctc ctg agc tgc caa gcc gac agc tac aag tac gag cat    1780
Gln Pro Val Leu Leu Ser Cys Gln Ala Asp Ser Tyr Lys Tyr Glu His
            575                 580                 585


ctg cgc tgg tac cgc ctc aac ctg tcc acg ctg cac gat gcg cac ggg    1828
Leu Arg Trp Tyr Arg Leu Asn Leu Ser Thr Leu His Asp Ala His Gly
        590                 595                 600

aac ccg ctt ctg ctc gac tgc aag aac gtg cat ctg ttc gcc acc cct    1876
Asn Pro Leu Leu Leu Asp Cys Lys Asn Val His Leu Phe Ala Thr Pro
    605                 610                 615

ctg gcc gcc agc ctg gag gag gtg gca cct ggg gcg cgc cac gcc acg    1924
Leu Ala Ala Ser Leu Glu Glu Val Ala Pro Gly Ala Arg His Ala Thr
620                 625                 630                 635

ctc agc ctg agt atc ccc cgc gtc gcg ccc gag cac gag ggc cac tat    1972
Leu Ser Leu Ser Ile Pro Arg Val Ala Pro Glu His Glu Gly His Tyr
                640                 645                 650

gtg tgc gaa gtg caa gac cgg cgc agc cat gac aag cac tgc cac aag    2020
Val Cys Glu Val Gln Asp Arg Arg Ser His Asp Lys His Cys His Lys
            655                 660                 665

aag tac ctg tcg gtg cag gcc ctg gaa gcc cct cgg ctc acg cag aac    2068
Lys Tyr Leu Ser Val Gln Ala Leu Glu Ala Pro Arg Leu Thr Gln Asn
        670                 675                 680

ttg acc gac ctc ctg gtg aac gtg agc gac tcg ctg gag atg cag tgc    2116
Leu Thr Asp Leu Leu Val Asn Val Ser Asp Ser Leu Glu Met Gln Cys
    685                 690                 695

ttg gtg gcc gga gcg cac gcg ccc agc atc gtg tgg tac aaa gac gag    2164
Leu Val Ala Gly Ala His Ala Pro Ser Ile Val Trp Tyr Lys Asp Glu
700                 705                 710                 715

agg ctg ctg gag gaa aag tct gga gtc gac ttg gcg gac tcc aac cag    2212
Arg Leu Leu Glu Glu Lys Ser Gly Val Asp Leu Ala Asp Ser Asn Gln
                720                 725                 730

aag ctg agc atc cag cgc gtg cgc gag gag gat gcg gga cgc tat ctg    2260
Lys Leu Ser Ile Gln Arg Val Arg Glu Glu Asp Ala Gly Arg Tyr Leu
            735                 740                 745
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tgc agc gtg tgc aac gcc aag ggc tgc gtc aac tcc tcc gcc agc gtg     2308
Cys Ser Val Cys Asn Ala Lys Gly Cys Val Asn Ser Ser Ala Ser Val
        750                 755                 760

gcc gtg gaa ggc tcc gag gat aag ggc agc atg gag atc gtg atc ctt     2356
Ala Val Glu Gly Ser Glu Asp Lys Gly Ser Met Glu Ile Val Ile Leu
    765                 770                 775

gtc ggt acc ggc gtc atc gct gtc ttc ttc tgg gtc ctc ctc ctc ctc     2404
Val Gly Thr Gly Val Ile Ala Val Phe Phe Trp Val Leu Leu Leu Leu
780                 785                 790                 795

atc ttc tgt aac atg agg agg ccg gcc cac gca gac atc aag acg ggc     2452
Ile Phe Cys Asn Met Arg Arg Pro Ala His Ala Asp Ile Lys Thr Gly
                800                 805                 810

tac ctg tcc atc atc atg gac ccc ggg gag gtg cct ctg gag gag caa     2500
Tyr Leu Ser Ile Ile Met Asp Pro Gly Glu Val Pro Leu Glu Glu Gln
            815                 820                 825

tgc gaa tac ctg tcc tac gat gcc agc cag tgg gaa ttc ccc cga gag     2548
Cys Glu Tyr Leu Ser Tyr Asp Ala Ser Gln Trp Glu Phe Pro Arg Glu
        830                 835                 840


cgg ctg cac ctg ggg aga gtg ctc ggc tac ggc gcc ttc ggg aag gtg     2596
Arg Leu His Leu Gly Arg Val Leu Gly Tyr Gly Ala Phe Gly Lys Val
    845                 850                 855

gtg gaa gcc tcc gct ttc ggc atc cac aag ggc agc agc tgt gac acc     2644
Val Glu Ala Ser Ala Phe Gly Ile His Lys Gly Ser Ser Cys Asp Thr
860                 865                 870                 875

gtg gcc gtg aaa atg ctg aaa gag ggc gcc acg gcc agc gag cac cgc     2692
Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr Ala Ser Glu His Arg
                880                 885                 890

gcg ctg atg tcg gag ctc aag atc ctc att cac atc ggc aac cac ctc     2740
Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly Asn His Leu
            895                 900                 905

aac gtg gtc aac ctc ctc ggg gcg tgc acc aag ccg cag ggc ccc ctc     2788
Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gln Gly Pro Leu
        910                 915                 920

atg gtg atc gtg gag ttc tgc aag tac ggc aac ctc tcc aac ttc ctg     2836
Met Val Ile Val Glu Phe Cys Lys Tyr Gly Asn Leu Ser Asn Phe Leu
    925                 930                 935

cgc gcc aag cgg gac gcc ttc agc ccc tgc gcg gag aag tct ccc gag     2884
Arg Ala Lys Arg Asp Ala Phe Ser Pro Cys Ala Glu Lys Ser Pro Glu
940                 945                 950                 955

cag cgc gga cgc ttc cgc gcc atg gtg gag ctc gcc agg ctg gat cgg     2932
Gln Arg Gly Arg Phe Arg Ala Met Val Glu Leu Ala Arg Leu Asp Arg
                960                 965                 970

agg cgg ccg ggg agc agc gac agg gtc ctc ttc gcg cgg ttc tcg aag     2980
Arg Arg Pro Gly Ser Ser Asp Arg Val Leu Phe Ala Arg Phe Ser Lys
            975                 980                 985

acc gag ggc gga gcg agg cgg gct tct cca gac caa gaa gct gag gac     3028
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Thr Glu Gly Gly Ala Arg Arg Ala Ser Pro Asp Gln Glu Ala Glu Asp
990 995 1000

ctg tgg ctg agc ccg ctg acc atg gaa gat ctt gtc tgc tac agc ttc 3076
Leu Trp Leu Ser Pro Leu Thr Met Glu Asp Leu Val Cys Tyr Ser Phe
1005 1010 1015

cag gtg gcc aga ggg atg gag ttc ctg gct tcc cga aag tgc atc cac 3124
Gln Val Ala Arg Gly Met Glu Phe Leu Ala Ser Arg Lys Cys Ile His
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aga gac ctg gct gct cgg aac att ctg ctg tcg gaa agc gac gtg gtg 3172
Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Ser Asp Val Val
1040 1045 1050

aag atc tgt gac ttt ggc ctt gcc cgg gac atc tac aaa gac cct gac 3220
Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp Pro Asp
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tac gtc cgc aag ggc agt gcc cgg ctg ccc ctg aag tgg atg gcc cct 3268
Tyr Val Arg Lys Gly Ser Ala Arg Leu Pro Leu Lys Trp Met Ala Pro
1070 1075 1080

gaa agc atc ttc gac aag gtg tac acc acg cag agt gac gtg tgg tcc 3316
Glu Ser Ile Phe Asp Lys Val Tyr Thr Thr Gln Ser Asp Val Trp Ser
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ttt ggg gtg ctt ctc tgg gag atc ttc tct ctg ggg gcc tcc ccg tac 3364
Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser Pro Tyr
1100 1105 1110 1115

cct ggg gtg cag atc aat gag gag ttc tgc cag cgg ctg aga gac ggc 3412
Pro Gly Val Gln Ile Asn Glu Glu Phe Cys Gln Arg Leu Arg Asp Gly
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aca agg atg agg gcc ccg gag ctg gcc act ccc gcc ata cgc cgc atc 3460
Thr Arg Met Arg Ala Pro Glu Leu Ala Thr Pro Ala Ile Arg Arg Ile
1135 1140 1145

atg ctg aac tgc tgg tcc gga gac ccc aag gcg aga cct gca ttc tcg 3508
Met Leu Asn Cys Trp Ser Gly Asp Pro Lys Ala Arg Pro Ala Phe Ser
1150 1155 1160

gag ctg gtg gag atc ctg ggg gac ctg ctc cag ggc agg ggc ctg caa 3556
Glu Leu Val Glu Ile Leu Gly Asp Leu Leu Gln Gly Arg Gly Leu Gln
1165 1170 1175

gag gaa gag gag gtc tgc atg gcc ccg cgc agc tct cag agc tca gaa 3604
Glu Glu Glu Glu Val Cys Met Ala Pro Arg Ser Ser Gln Ser Ser Glu
1180 1185 1190 1195

gag ggc agc ttc tcg cag gtg tcc acc atg gcc cta cac atc gcc cag 3652
Glu Gly Ser Phe Ser Gln Val Ser Thr Met Ala Leu His Ile Ala Gln
1200 1205 1210

gct gac gct gag gac agc ccg cca agc ctg cag cgc cac agc ctg gcc 3700
Ala Asp Ala Glu Asp Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala
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gcc agg tat tac aac tgg gtg tcc ttt ccc ggg tgc ctg gcc aga ggg 3748
Ala Arg Tyr Tyr Asn Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly

1230 1235 1240

gct gag acc cgt ggt tcc tcc agg atg aag aca ttt gag gaa ttc ccc 3796
Ala Glu Thr Arg Gly Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro
1245 1250 1255

atg acc cca acg acc tac aaa ggc tct gtg gac aac cag aca gac agt 3844
Met Thr Pro Thr Thr Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser
1260 1265 1270 1275

ggg atg gtg ctg gcc tcg gag gag ttt gag cag ata gag agc agg cat 3892
Gly Met Val Leu Ala Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg His
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aga caa gaa agc ggc ttc agg tagctgaagc agagagagag aaggcagcat 3943
Arg Gln Glu Ser Gly Phe Arg
1295

acgtcagcat tttcttctct gcacttataa gaaagatcaa agactttaag actttcgcta 4003

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gaaagtggac aaggagtgtg accactgaag caccacaggg aaggggttag gcctccggat 4123

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20 25 30

Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser
35 40 45

Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala
50 55 60

Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val
65 70 75 80

Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu
85 90 95

Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr
100 105 110

Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser
115 120 125

Tyr Val Phe Val Arg Asp Phe Glu Gln Pro Phe Ile Asn Lys Pro Asp
130 135 140

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Thr Leu Leu Val Asn Arg Lys Asp Ala Met Trp Val Pro Cys Leu Val
145                 150                 155                 160

Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu
                165                 170                 175

Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu
            180                 185                 190

Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr
        195                 200                 205

Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile
    210                 215                 220

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225                 230                 235                 240

Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp Ala
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Glu Ser Thr Glu Val Ile Val His Glu Asn Pro Phe Ile Ser Val Glu
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Trp Leu Lys Gly Pro Ile Leu Glu Ala Thr Ala Gly Asp Glu Leu Val
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Lys Leu Pro Val Lys Leu Ala Ala Tyr Pro Pro Pro Glu Phe Gln Trp
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Tyr Lys Asp Gly Lys Ala Leu Ser Gly Arg His Ser Pro His Ala Leu
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Val Leu Lys Glu Val Thr Glu Ala Ser Thr Gly Thr Tyr Thr Leu Ala
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Leu Trp Asn Ser Ala Ala Gly Leu Arg Arg Asn Ile Ser Leu Glu Leu
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Val Val Asn Val Pro Pro Gln Ile His Glu Lys Glu Ala Ser Ser Pro
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Ser Ile Tyr Ser Arg His Ser Arg Gln Ala Leu Thr Cys Thr Ala Tyr
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Gly Val Pro Leu Pro Leu Ser Ile Gln Trp His Trp Arg Pro Trp Thr
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995 1000 1005

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1125 1130 1135

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<211> 14

<212> PRT

<213> Homo sapiens

<400> 33

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1 5 10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:
60/326,326 1 October 2001 (01.10.2001) US

(71) Applicants (*for all designated States except US*): **LUDWIG INSTITUTE FOR CANCER RESEARCH** [US/US]; 605 Third Avenue, New York, NY 10158 (US). **LICENTIA LTD** [FI/FI]; Erottajankatu 19B, 6th Floor, FIN-00130 Helsinki (FI).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **ALITALO, Kari** [FI/FI]; Molceular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARKKAINEN, Marika** [FI/FI]; Molceular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARILA, Kaisa** [FI/NL]; Merelstraat 40, NL-2333 XM Leiden (NL).

(74) Agents: **JUMP, Timothy** et al.: Venner, Shipley & Co., 20 Little Britain, London EC1A 7DH (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 31 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS

(57) Abstract: The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

WO 2003/029814 A3

INTERNATIONAL SEARCH REPORT

In al Application No
PCT/EP 02/11069

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/50 G01N33/74 C07K16/46 C07K14/475

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 23565 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 27 April 2000 (2000-04-27) page 1 - page 11 claims 4-21 -----	1-18, 26-30, 33-38
Y	WO 99 29729 A (CHILDREN'S MEDICAL CENTER CORPORATION) 17 June 1999 (1999-06-17) the whole document -----	1-18, 26-30, 33-38
Y	WO 01 09157 A (NEXSTAR PHARMACEUTICALS, INC.) 8 February 2001 (2001-02-08) page 1, line 20 - page 8, line 20 ----- -/--	1-18, 26-30, 33-38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2003	03.11.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giry, M.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 07832 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 26 February 1998 (1998-02-26) claims 37-77; example 7 -----	1-18, 26-30, 33-38
Y	WO 01 31346 A (PROCTER & GAMBLE COMPANY) 3 May 2001 (2001-05-03) page 1, line 5 - page 6, line 21 page 12, line 25 - page 13, line 33 example 7 claims 1-11 -----	16,17
Y	WO 00 21560 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 20 April 2000 (2000-04-20) page 83, line 19 - page 84, line 14 examples 15-17	12,13, 16,17
Y	page 87, line 10 - line 20 -----	29,30
A	ACHEN M.G. ET AL.: "Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3." EUR. J. BIOCHEM., vol. 267, 2000, pages 2505-2515, XP002247239 the whole document -----	
A	BAGNARD D. ET AL.: "Semaphorin 3A-vascular endothelial growth factor-165 balance mediates migration and apoptosis of neural progenitor cells by the recruitment of shared receptor." J. NEUROSC., vol. 21, no. 10, 15 May 2001 (2001-05-15), pages 3332-3341, XP001057926 the whole document -----	
P,X	KARKKAINEN M.J. ET AL.: "Lymphatic endothelium : a new frontier of metastasis research." NATURE CELL BIOLOGY, vol. 4, January 2002 (2002-01), pages E2-E5, XP002247240 the whole document -----	1-18, 26-30, 33-38

INTERNATIONAL SEARCH REPORT	...ational application No. PCT/EP 02/11069

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3, 26-29, 33-37
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3, 26-29, and 33-37, due to the step of administering a composition, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18, 26-30, 33-38

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 3, 26-29, 33-37

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18, 26-30, 33-38

Methods and peptidic compounds relating to the ability of VEGF-C to bind to neuropilin.

---

2. claims: 19-25, 31-32

Methods and peptidic compounds relating to the ability of VEGFR-3 to bind to neuropilin.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/11069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0023565 A	27-04-2000	AU 1123700 A	08-05-2000
		CA 2346798 A1	27-04-2000
		CN 1324242 T	28-11-2001
		EP 1124570 A2	22-08-2001
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WO 9929729 A	17-06-1999	AU 1633999 A	28-06-1999
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		WO 0021560 A1	20-04-2000

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International Bureau

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(51) International Patent Classification[7]: G01N 33/50, 33/74, C07K 16/46, 14/475

(21) International Application Number: PCT/EP2002/011069

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/326,326 1 October 2001 (01.10.2001) US

(71) Applicants (*for all designated States except US*): **LUDWIG INSTITUTE FOR CANCER RESEARCH** [US/US]; 605 Third Avenue, New York, NY 10158 (US). **LICENTIA LTD** [FI/FI]; Erottajankatu 19B, 6th Floor, FIN-00130 Helsinki (FI).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **ALITALO, Kari** [FI/FI]; Molceular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARKKAINEN, Marika** [FI/FI]; Molceular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARILA, Kaisa** [FI/NL]; Merelstraat 40, NL-2333 XM Leiden (NL).

(74) Agents: JUMP, Timothy et al.; Venner, Shipley & Co., 20 Little Britain, London EC1A 7DH (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *with amended claims*

(88) Date of publication of the international search report: 31 December 2003

Date of publication of the amended claims: 18 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/029814 A3

(54) Title: NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS

(57) Abstract: The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

AMENDED CLAIMS
[received by the International Bureau on 02 January 2004 (02.01.04) ;
original claims 1-38 replaced by amended claims 1-37 (9 pages)]

What is claimed is:

1. A method of screening for modulators of binding between a neuropilin-2 growth factor receptor and a VEGF-C polypeptide, comprising steps of:

a) contacting a neuropilin-2 composition that comprises a neuropilin-2 polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin-2 polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin-2 polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

2. A method according to claim 1, further comprising a step of:

(d) making a modulator composition by formulating a modulator identified according to step (c) in a pharmaceutically acceptable carrier.

3. A method according to claim 2, further comprising:

(e) administering the modulator composition to an animal that comprises cells that express the neuropilin-2 receptor, and determining physiological effects of the modulator composition in the animal.

4. A method according to any one of claims 1-3 wherein the neuropilin-2 composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a neuropilin-2 receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing neuropilin-2 polypeptides; and

(c) a cell recombinantly modified to express increased levels of

neuropilin-2 receptor polypeptide on the cell surface.

5. A method according to any one of claims 1-3, wherein the neuropilin-2 composition comprises a polypeptide comprising a neuropilin-2 receptor extracellular domain fragment bound to a solid support.

6. A method according to claim 1, wherein the neuropilin-2 polypeptide comprises a neuropilin-2 receptor extracellular domain fragment fused to an immunoglobulin Fc fragment.

7. A method according to any one of claims 1-6 , wherein the neuropilin-2 polypeptide is human.

8. A method according to any one of claims 1-6 wherein the neuropilin-2 polypeptide comprises an amino acid sequence at least 90% identical to: the amino acid sequence set forth in SEQ ID NO: 4 or a fragment thereof that binds VEGF-C.

9. A method according to any one of claims 1-8 wherein the VEGF-C polypeptide comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment of the prepro-VEGF-C polypeptide, that binds the neuropilin-2 receptor.

10. A method according to claim 9, wherein the prepro-VEGF-C polypeptide is human.

11. A method according to any one of claims 1-8 wherein the VEGF-C polypeptide comprises an amino acid sequence at least 90% identical to: the amino acid sequence set forth in SEQ ID NO: 24 or a fragment thereof that binds neuropilin-2.

12. A method according to any one of claims 1-8, wherein the VEGF-C polypeptide comprises a fragment of human prepro-VEGF-C that contains amino acids 103-227 of SEQ ID NO: 24.

13. A method according to any one of claims 1-8, wherein the VEGF-C polypeptide comprises amino acids 32 to 227 of the human prepro-VEGF-C sequence of SEQ. ID. NO: 24.

14. A method according to any one of claims 1-8, wherein the VEGF-C composition comprises a conditioned media from a cell recombinantly modified to express and secrete a VEGF-C polypeptide.

15. A method according to any one of claims 1-3, wherein the neuropilin-2 composition comprises a cell recombinantly modified to express increased amounts of a neuropilin-2 receptor on its surface, and wherein the detecting step comprises measuring a VEGF-C binding-induced physiological change in the cell.

16. A method for screening for selectivity of a modulator of VEGF-C biological activity, comprising steps of:

a) contacting a VEGF-C composition with a neuropilin-2 composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin-2 in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the neuropilin-2;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGFR-3 extracellular domain; and

(ii) a polypeptide comprising a VEGFR-2 extracellular domain; and

(c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

17. A method for screening for selectivity of a modulator of neuropilin-2 biological activity, comprising steps of:

a) contacting a neuropilin-2 composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin-2 and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin-2 and the VEGF-C;

b) contacting a neuropilin-2 composition with a composition comprising a neuropilin-2 binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin-2 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin-2 and the binding partner; and wherein the binding partner is a polypeptide comprising an amino acid sequence selected from the group consisting of:

an amino acid sequence of a semaphorin 3 polypeptide; a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and an amino acid sequence of a plexin polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

18. A method according to claim 17 wherein the binding partner is a human semaphorin.

19. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

20. A method according to claim 19 wherein the VEGFR-3 composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a VEGFR-3 receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing VEGFR-3 polypeptides; and

(c) a cell recombinantly modified to express increased levels of VEGFR-3 receptor on the cell surface.

21. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment bound to a solid support.

22. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment fused to an immunoglobulin Fc fragment.

23. A method according to any one of claims 19-22, wherein the VEGFR-3 is a mammalian VEGFR-3.

24. A method according to claim 23, wherein the VEGFR-3 is human.

25. A method for screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of the compound and detecting binding between the VEGFR-3 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and

(ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

26. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a neuropilin-2 polypeptide or fragment thereof that binds to VEGF-C polypeptide expressed in the mammalian organism;

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin-2 in the mammalian organism.

27. A method according to claim 26, wherein the mammalian organism is human.

28. A method according to claim 26, further comprising administering a second agent to the patient for modulating endothelial growth, migration, or proliferation through a neuropilin-2 receptor, said second agent comprising a polypeptide comprising an amino acid sequence selected from the group consisting of: a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a VEGF-E amino acid sequence, a PlGF amino acid sequence, a semaphorin 3A amino acid sequence, semaphorin 3C amino acid sequence, and a semaphorin 3F amino acid sequence.

29. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin-2 receptor and for a VEGF-C polypeptide expressed in the mammalian organism,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin-2 receptor in the mammalian organism.

30. A bispecific antibody which specifically binds to a neuropilin-2 receptor and a VEGF-C polypeptide.

31. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor and a VEGFR-3 polypeptide; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and the VEGFR-3 polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor and the VEGFR-3 polypeptide in the mammalian organism.

32. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGFR-3 polypeptide.

33. A method of modulating neuronal growth, or neuronal scarring in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin-2 receptor.

34. A method according to claim 33, wherein the mammalian organism is human.

35. A method according to any one of claims 33-34, wherein the organism has a disease characterized by aberrant growth of neuronal cells involved in scarring and neural degeneration.

36. A method according to claim 35, wherein the disease comprises a neurodegenerative disorder, more specifically Alzheimer's disease.

37. A polypeptide comprising a VEGF-C polypeptide or a fragment thereof that binds to a neuropilin-2 receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin-2 receptor.